Electronic effects in the Diels-Alder reaction: towards catalytic chiral auxiliaries

Durrant, Steven

Award date:
2002

Awarding institution:
University of Bath

Electronic Effects in the Diels-Alder Reaction: Towards Catalytic Chiral Auxiliaries

Submitted by Steven Durrant

for the degree of PhD

of the University of Bath

May 2002

S.J. Durrant

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Abstract

The use of chiral auxiliaries in organic synthesis is widely documented. However, their use is not without its limitations. This thesis describes approaches towards developing methodology for the use of catalytic chiral auxiliaries.

The review in chapter one describes the utility of chiral auxiliaries in asymmetric Diels-Alder reactions.

The second chapter details attempts to utilise the electronic differences between α,β-unsaturated carboxylates and α,β-unsaturated esters to obtain a cycle whereby chiral auxiliaries can be used in a catalytic manner. The palladium catalysed allylic substitution reaction is utilised as a key step.

Oxazolidinones have been widely used as chiral auxiliaries, and research towards exploiting the greater reactivity of α,β-unsaturated oxazolidinyl substrates versus α,β-unsaturated esters is described.

Allylic alcohols do not act as dienophiles in the Diels-Alder reaction. However, temporary activation as the corresponding ketone allows this "impossible" reaction to occur. This research is outlined in chapter four.

Acknowledgements

I would firstly like to thank my supervisor, Prof. Jonathon Williams for all his help, encouragement and guidance throughout my PhD. It has been a privilege to work for Jon and I have a great deal to thank him for.

I would also like to thank my industrial supervisor Dr. Dave Colclough for all his guidance and comments on the project. In addition, I would like to thank GlaxoSmithKline for funding this project and the members of DC1 at Dartford for making my time there so memorable.

It has been my pleasure to work with some most interesting people at the University of Bath, and I would like to thank them, in no particular order, for their friendship, help and for making my time at Bath so enjoyable; Lara, Tim, J-P, Cath, Steve, Mike, Gian, Matt, Mark, Parminder, Becky, Alison, Christelle, Joe, Phil B, Phil P, Fred, Claudia, Mike E, Kokovi, Kerry, Christian, Vincent, Suvi, Stav, and Paul.

Special thanks must also go to my fiancée Lara. Thank you for all your love and help. I couldn't have done it without you.

Finally I would like to thank my family for all their love and support over the years. Thank you Dad, Mum and Tony.

Abbreviations

Ac	Acetate
Aux*H	Chiral Auxiliary
BSA	*N,O*-Bis(trimethylsilyl)acetamide
CAN	Ceric ammonium nitrate
COD	1,5-Cyclooctadiene
CpH	Cyclopentadiene
DABCO	1,4-Diazobicyclo[2.2.2]octane
DBA	*trans,trans*-Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]non-5-ene
DCE	Dichloroethane
DCM	Dichloromethane
d.e.	Diastereomeric Excess
DMAP	4-(Dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPPE	1,2-Bis(diphenylphosphino)ethane
d.r.	Diastereomeric Ratio
EDG	Electron Donating Group
Eq.	Equivalents
EtOAc	Ethyl Acetate
EtOH	Ethanol
EWG	Electron Withdrawing Group
GC	Gas Chromatography

HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IR	Infra Red
IS	Internal Standard
k	Rate constant for reaction
Ln	Ligand
LUMO	Lowest Unoccupied Molecular Orbital
MeCN	Acetonitrile
MeOH	Methanol
MPV	Meerwein-Ponndorf-Verley
MVK	Methyl vinyl ketone
NMR	Nuclear Magnetic Resonance
PhOH	Phenol
Piv	Pivalate
PPTS	Pyridinium *p*-toluenesulfonate
RT	Room Temperature
$[SM]_0$	Concentration of starting material at start of reaction
$[SM]_t$	Concentration of starting material at a certain time, t
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Triflate	Trifluromethanesulfonate

Contents

Chapter 1

Chiral Auxiliaries in the Diels-Alder Reaction

1) Chiral Auxiliaries in the Diels-Alder Reaction

1.1 Introduction

Discovered in 1928 by Otto Diels and Kurt Alder,[1] the reaction that now bears their name is an example of a general class of cycloaddition reactions that have become arguably one of the most powerful carbon-carbon bond forming processes.[2] The Diels-Alder reaction occurs between a diene **1** and an alkene, commonly called the dienophile, **2** to form a cyclohexene ring **3**.

1 **2** **3**

Scheme 1

During this reaction two new carbon-carbon single bonds are formed at the expense of two double bonds providing a significant driving force for the reaction. By substitution of a carbon atom from either the diene or the dienophile with a heteroatom, heterocyclic compounds can be formed.[3] In addition, the reaction is a useful tool in natural product synthesis.[4]

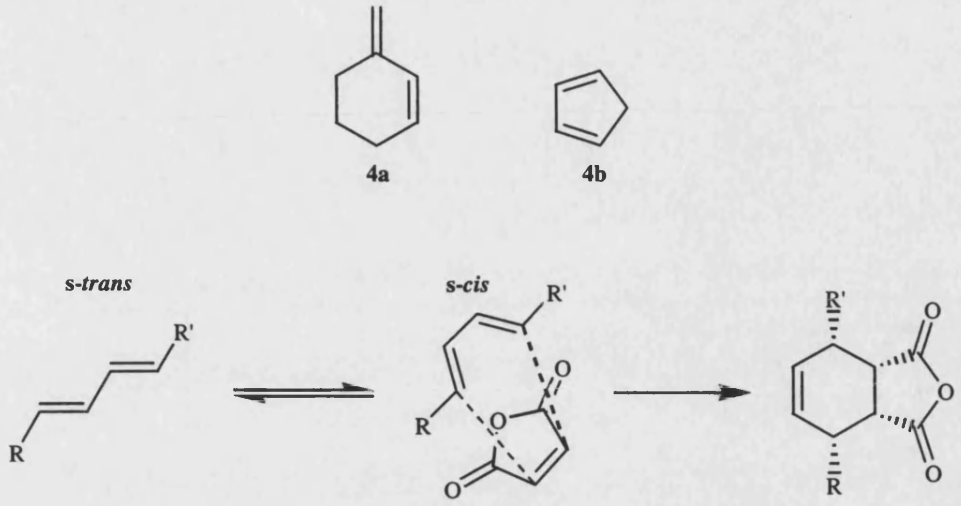
As the reaction involves four π electrons from the diene and two π electrons from the dienophile, it is classed as a [$4\pi + 2\pi$] cycloaddition. Various experimental details suggest the reaction proceeds *via* a concerted mechanism. Many of the mechanistic details can be explained by invoking Molecular Orbital theory.

1.2 Mechanistic Considerations

Although the reaction does occur in the unsubstituted case, albeit under very harsh conditions,[5] it proceeds more readily when the diene and dienophile contain

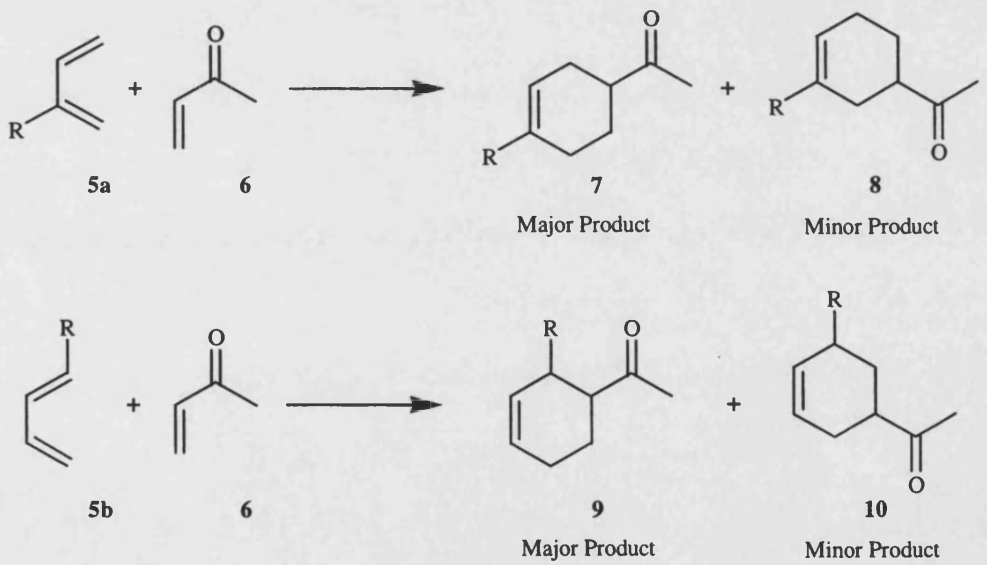
substituents of opposite electronic influence. Most Diels-Alder reactions involve a diene with an electron-donating substituent, such as an alkyl or alkoxy group, and a dienophile bearing an electron-withdrawing group, for example a carbonyl or nitrile. When the substituents are reversed the reaction is said to proceed under inverse electron demand.

As the reaction proceeds *via* a concerted, although not necessarily synchronous, manner the diene must adopt the s-*cis* (cisoid) conformation. Hence dienes with one double bond exocyclic, such as **4a**, do not react, but endocyclic dienes **4b**, which are fixed in the s-*cis* conformation react rapidly. Most open chain dienes prefer to adopt the s-*trans* conformation (for example butadiene prefers s-*trans* over s-*cis* by 13 kJ mol $^{-1}$)[6] and their reactivity depends on the interconversion of the two forms. Experimentally, a *cis*-1-substituent favours the s-*trans* form and retards the reaction, whereas a 2-substituent favours the s-*cis* form and enhances the reaction. In addition, Diels-Alder reactions are generally stereospecific, *i.e.* the configurations of both diene and dienophile are preserved in the final product, which again supports the proposed transition state evidence. This is consistent with a concerted transition state where bonding occurs simultaneously at both ends of the diene.



Scheme 2

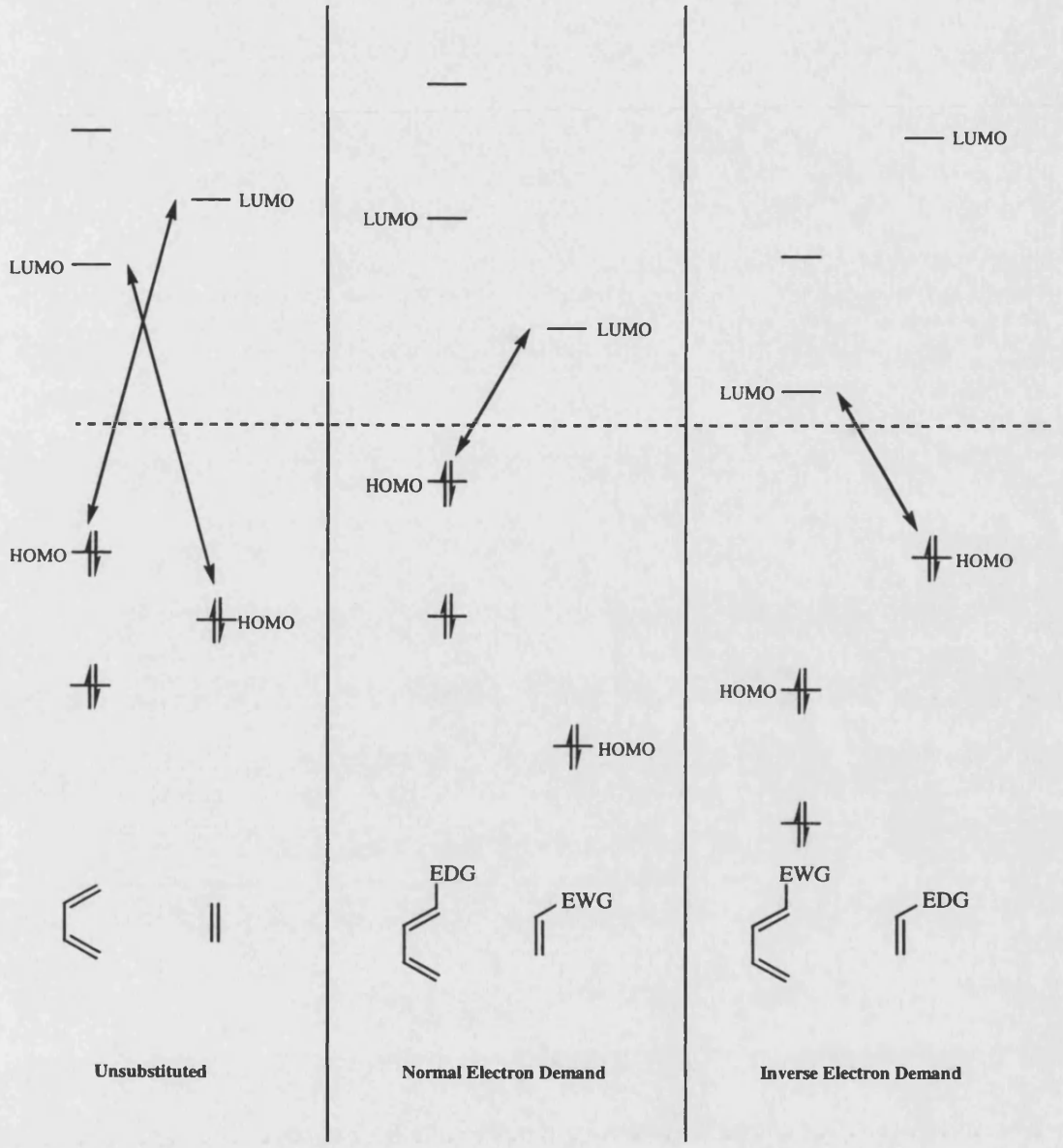
When both the diene and dienophile are mono-substituted, regioisomers are formed (**Scheme 3**). The selectivity of the reactions and the tendency for electron-donating groups on the diene and electron-withdrawing groups on the dienophile to enhance the rate of reaction can be explained using Frontier Molecular Orbital theory.[7]



Scheme 3

Many of the fine mechanistic details of the Diels-Alder reaction can be explained by looking at the interactions between the HOMO and LUMO π energy levels of the reacting diene and dienophile that are closest in energy. The energy levels for

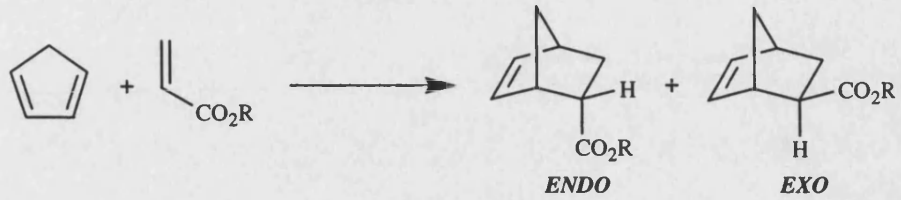
butadiene and ethylene are shown in **Scheme 4**. In a normal electron demand reaction, adding an electron-donating substituent raises the HOMO of the diene whereas the LUMO of the dienophile is lowered by the addition of an electron-withdrawing group. The net result is an increased interaction between the two frontier orbitals and hence a more efficient reaction. In an inverse electron demand case, the HOMO of the dienophile is raised and the LUMO of the diene is lowered, making this the dominant interaction. This model is consistent with the use of a Lewis acid to promote reaction, as its coordination to a carbonyl group further lowers the LUMO of the dienophile.



Scheme 4

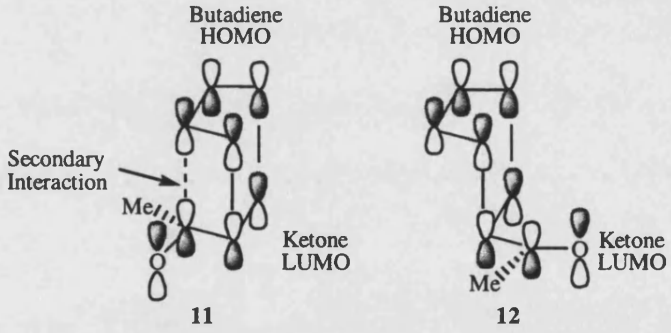
The regiochemical outcome of the reaction can be explained if it is assumed that the strongest interactions will occur between atoms that have the largest orbital coefficients. Dienophiles with electron-withdrawing groups have the largest coefficient at the β carbon. Dienes with electron-donating groups at C1 show the largest coefficient at C4 and for those with the substituent at C2, the largest coefficient is at C1. Hence, the preferential formation of the "para" product **7** can be explained by the combination of the dienophile β carbon and C1 of the diene.

When both the diene and the dienophile are substituted the *endo* principle applies.[8] As shown in **Scheme 5**, the major product is that formed from the transition state with the maximum combination of unsaturated centres.



Scheme 5

From a frontier orbital perspective, *secondary interactions* are important. Of the two possible transition states for the reaction between butadiene and methyl vinyl ketone, intermediate **11** is further stabilised by interaction between orbitals on the carbonyl group and the diene. This can be ascribed to overlap of orbitals of matching symmetry on the carbonyl carbon and C2 of the diene. The dienophile reacts as a 2π system but is actually part of a 4π system. The LUMO of this 4π system has the correct symmetry for both primary and secondary orbital overlap with the HOMO of the diene.



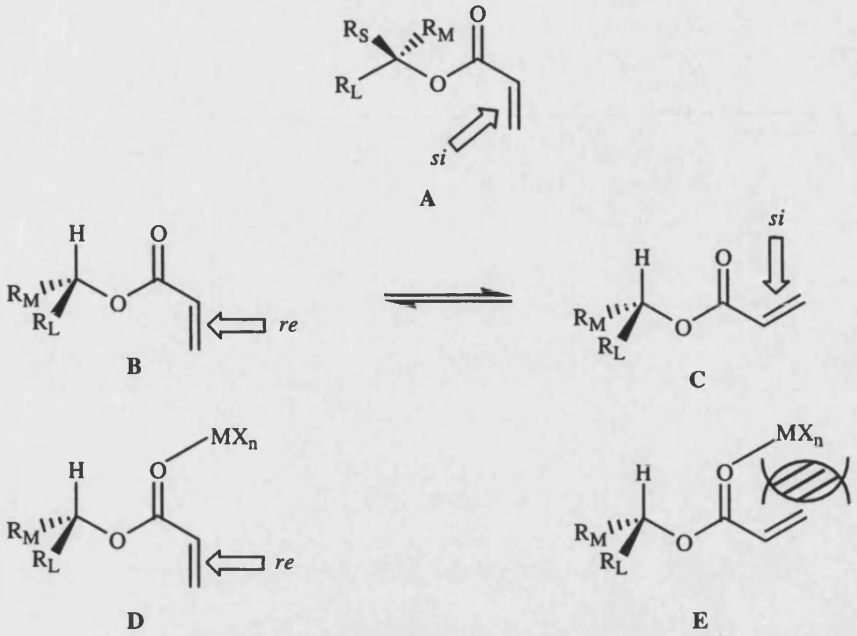
Scheme 6

Selectivity for the *endo* product is reduced when the dienophile bears an α-substituent. The reaction between cyclopentadiene and methyl methacrylate yields a product where the *endo*:*exo* ratio is 3:7. The methyl group has its own attractive secondary interaction with the diene and can compete with the carbonyl for the *endo* position. The use of Lewis acid catalysis not only enhances the rate of reaction, but also can improve selectivity for the *endo* product. When the methyl methacrylate reaction is

run in the presence of $AlCl_3$, the *endo*:*exo* ratio changes to 6:4. This can be accounted for by an augmented secondary interaction. Coordination of the Lewis acid increases the orbital coefficient at the carbonyl carbon and hence increases the magnitude of the overlap. Utilisation of other solvents, pressure and salt effects can also affect the regiochemical outcome of the Diels-Alder reaction.[9]

1.3 Asymmetric Diels-Alder Reactions

For the Diels-Alder reaction to be synthetically useful, methodology must be developed to control which diastereomer of the product is produced. If either the diene or dienophile is enantiomerically enriched, the reaction can proceed in a facially selective manner to yield a mixture of diastereomers. The higher the level of facial control obtained, the more selective the reaction, until in an ideal case a single diastereomer is formed. Studies into the development of an asymmetric Diels-Alder reaction appeared as early as 1961, but it is only in the last two decades that substantial progress has been made. Two main methods have appeared over this time. The use of Lewis acids bearing enantiomerically pure ligands is particularly popular and has been reviewed extensively.[10] Alternatively a chiral auxiliary [11] group can be attached temporarily to the diene or dienophile, and later removed from the diastereomerically enriched intermediate to give an enantiomerically enriched product. The majority of this work has focused on dienophiles bearing chiral auxiliaries and in particular derivatives of α,β-unsaturated carbonyl compounds. Before any discussion of chiral auxiliaries is attempted, it is useful to appreciate the possible conformations of chiral acrylate esters and their effect on the stereochemical outcome of the reaction (**Scheme 7**).



Scheme 7

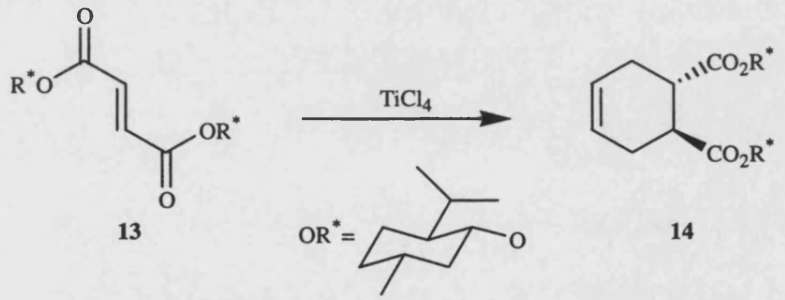
Conformation **A**, postulated by Prelog *et al.*,[12] implies an *anti*-orientation of the large substituent and the carbonyl group that is antiperiplanar to the double bond. Spectroscopic data suggest that in solution an equilibrium actually occurs between conformers **B** and **C**, with the former being favoured by only $\Delta H = 0.32$ kcal mol^{-1}. If the diene adds exclusively to the π-face opposite to the larger substituent, conformers **B** and **C** result in reversed topicity. Consistent with this, thermal Diels-Alder reactions do not show high levels of enantioselectivity.

When a Lewis acid is used the situation changes dramatically. Coordination occurs *anti* to the ester oxygen. Hence, conformer **E** is disfavoured on steric grounds and suggests reaction occurs *via* conformer **D**. As mentioned earlier, Lewis acids increase rates of reaction and *endo* selectivity. As a consequence, asymmetric Diels-Alder reactions are usually carried out at low temperatures in the presence of Lewis acids. As will be shown later, this hypothesis is only valid when the Lewis acid does not bind to R_M or R_L.

1.4 Auxiliaries based on secondary alcohols

1.4a Menthol and its derivatives as chiral auxiliaries

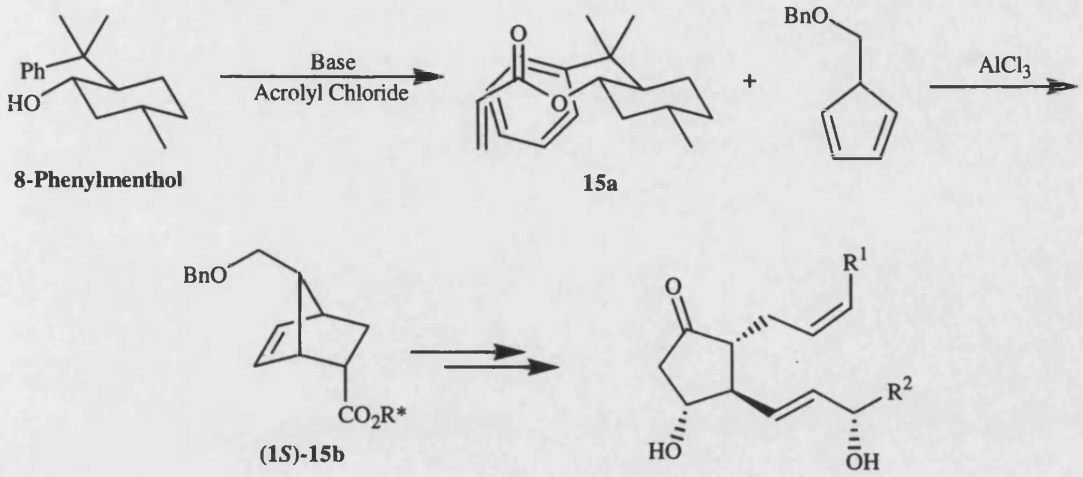
In 1963 Walborsky [13] published his pioneering work on the addition of bis(menthyl) fumarate **13** to 1,3-butadiene promoted by a variety of Lewis acids. Cyclohexene derivative **14** can be obtained in up to 80% yield and 78% d.e. when one equivalent of $TiCl_4$ is used in toluene at room temperature. This relatively high diastereoselectivity is not surprising since the fumarate profits from a cooperative influence of two chiral auxiliaries that increase its dienophilicity and direct the reaction to occur on the face opposite to the largest groups. However the utilisation of a single menthyl auxiliary shows much lower selectivity. For instance, the addition of menthyl acrylate to cyclopentadiene generates the desired cycloadduct in 65% yield and 62% d.e.[14]



Scheme 8

Corey and Ensley reported the first use of an asymmetric Diels-Alder reaction in an enantioselective synthesis in their research towards the synthesis of prostaglandins (**Scheme 9**).[15] When no chiral auxiliary is used, a racemic mixture of products (1*R*)-**15b** and (1*S*)-**15b** is formed. Only the (1*S*)-enantiomer is required for the synthesis of prostaglandins and hence exclusive diene addition from the C_α *re*-face is necessary. (-)-8-Phenylmenthol, which is readily available from the natural product (+)-pulegone, was utilised as the chiral auxiliary. π-Shielding of the C_α *si*-face of the acrylate **15a** forces reaction to occur on the desired C_α *re*-face and produced the desired

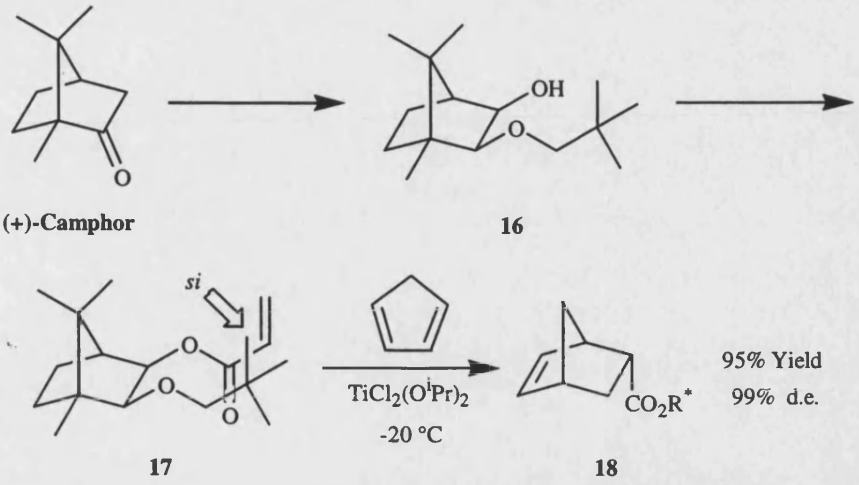
diastereomer with high selectivity. This was further elaborated to give a substituted cyclopentanone that has been used as a starting material for several different prostaglandins.



Scheme 9

The use of (-)-8-phenylmenthol is limited due to the need for careful purification during its preparation from (+)-pulegone. In addition, the oily nature of the cycloadduct intermediates makes further enhancement of the diastereoselectivity by recrystalisation impossible. For a chiral auxiliary to be generally useful the opposite enantiomer should be easily accessible and this is not the case for (-)-8-phenylmenthol.

Various conformationally rigid cyclohexanols have been investigated as chiral auxiliaries.[16] Some of the most useful are those based on camphor.[17] Both enantiomers of camphor are readily available and in addition its crystalline nature makes purification of its adducts easy.



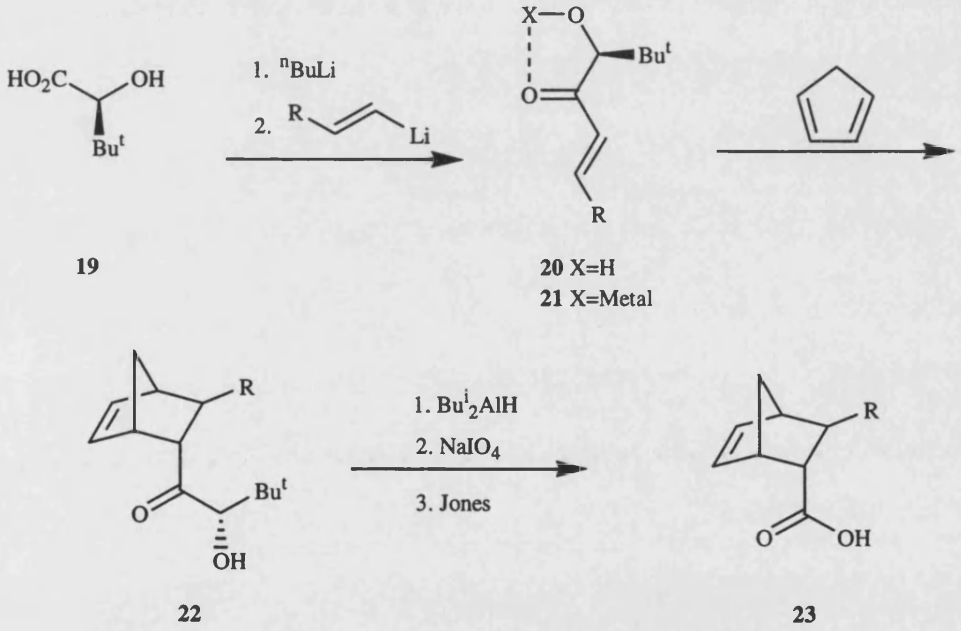
Scheme 10

The neopentyl ether **16** has been found to display a chirality directing effect greater than that of 8-phenylmenthol. Either enantiomer can be prepared in 60% overall yield from the requisite enantiomer of camphor. Reaction of the corresponding acrylate ester **17** with various dienes gives cycloadducts such as norbornene **18** in high yield and with 93 to 96% *endo*-selectivity and over 99% diastereofacial differentiation, due to steric blocking of a particular π-face by the neopentyl group (Conformer **17**). The auxiliaries can be removed non-destructively by reduction with $LiAlH_4$ and separated from products by column chromatography. However, when less reactive dienophiles are used the reaction is generally sluggish. For instance the addition of cyclopentadiene to **16**-crotonate leads preferentially to polymerisation.[18]

1.4b Chiral auxiliaries based on lactates and pantolactone

In an attempt to include the reaction of less active dienophiles, such as those containing β-substituents, to less reactive dienes, more activating auxiliaries are required. Chelation plays an important role in the reactivity of α-hydroxy ketone derivatives **20**.[19] Prepared by separation of acid **19** from its enantiomer followed by successive treatment with ^{n}BuLi and the appropriate vinyllithium reagent, the resultant

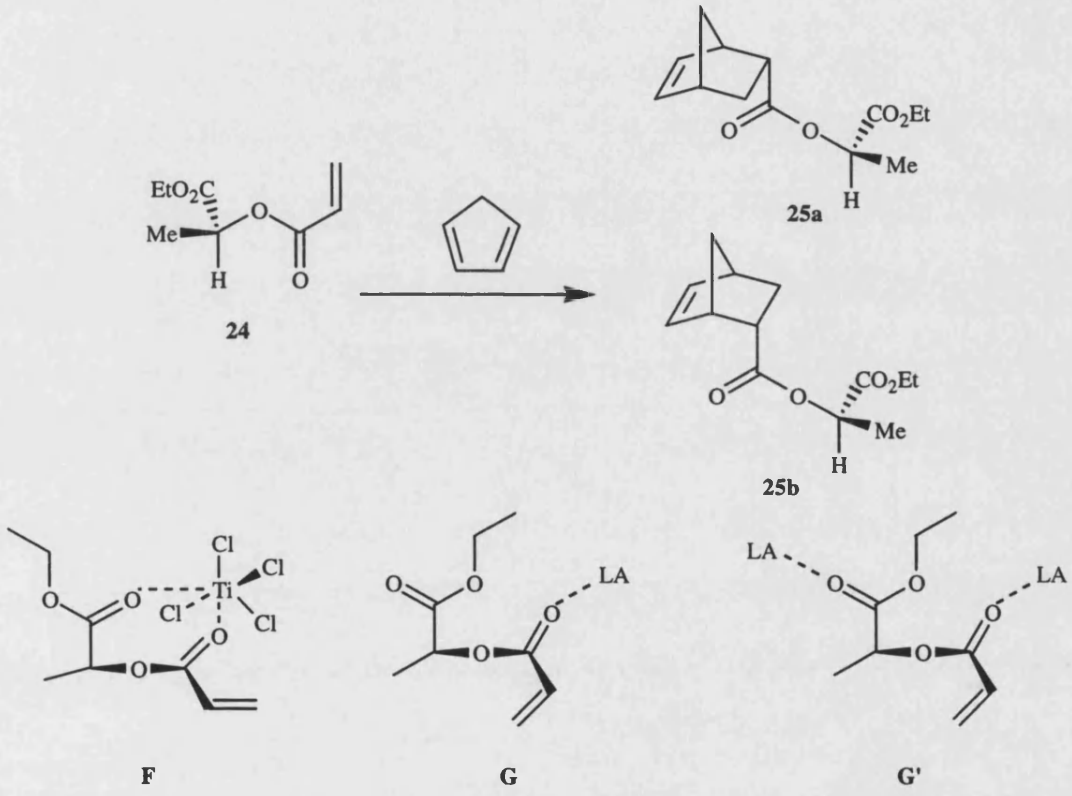
conjugated α-hydroxy ketones undergo Diels-Alder reaction with cyclopentadiene at –20 °C in the absence of a Lewis acid to give cycloadduct **22** with 99% diastereofacial discrimination. The high selectivity undoubtedly stems from hydrogen bonding which constrains the chiral centre within a five membered ring. The bulky *tert*-butyl group enforces the C=O/C=C *syn*-conformation and directs the diene to the opposite face of the enone. The hydrogen bond also accelerates the rate of reaction by lowering the LUMO of the dienophile. By addition of a Lewis acid such as $ZnCl_2$ or $Ti(O^iPr)_4$ the reaction proceeds at an even lower temperature and with higher selectivity. However, the destruction of the auxiliary upon oxidative removal (**22** to **23**) is an obvious limitation.



Scheme 11

In similar work the acrylates of (*S*)-ethyl lactate are effective dienophiles in the Lewis acid catalysed Diels-Alder reaction.[20] Interestingly when the addition of cyclopentadiene to acrylate **24** was carried out in the presence of $TiCl_4$, the product was isolated with 86% C_α-*si*-face selectivity. By changing the catalyst to $BF_3.OEt_2$ the topicity was reversed. These effects were explained by the determination of the single

crystal structure of a 1:1 acrylate:$TiCl_4$ complex.[21] Reaction of acrylate **24** with cyclopentadiene in the presence of $TiCl_4$ predominantly yields cycloadduct **25a**, formed as the *re* face of intermediate **F** is blocked by a chloride ligand. If more than one equivalent of $TiCl_4$ is used the diastereoselectivity drops considerably, suggesting the intermediacy of other non-chelated species **G** and **G'**. This is supported by the fact that Lewis acids disposed to four-coordination such as $EtAlCl_2$ or BF_3, induce preferential addition to the acrylate *re* face as is to be expected for **G** and **G'**.

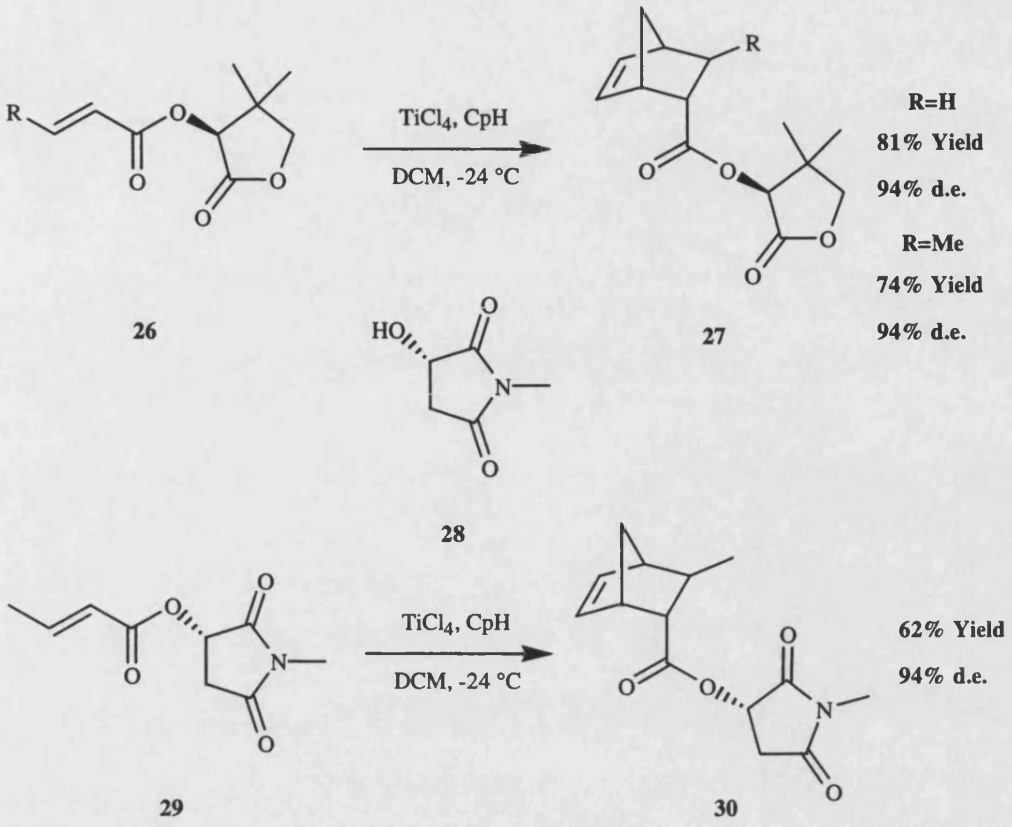


Scheme 12

It follows that if complex **F** can be stabilised relative to **G/G'**, the level of diastereoselectivity should be increased. From the crystal structure of **F**, the lactate backbone O-(CO)-C-Me shows a torsion angle of 20°. A cyclic structure should possess a coordination geometry similar to **F**, but the entropy balance with respect to competing monodentate complexes should be more favourable. As such,

commercially available (*R*)-pantolactone was selected as an equivalent to (*R*)-lactates.[22]

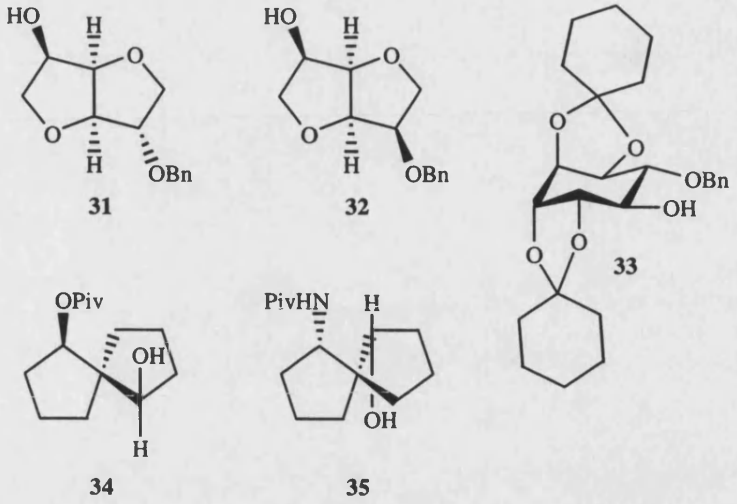
The $TiCl_4$ catalysed Diels-Alder reaction of acrylate **26** (R=H) proceeds in high diastereoselectivity with a wide variety of dienes. Remarkably, the reaction is particularly insensitive to reaction temperatures and proceeds smoothly in the presence of only catalytic amounts of $TiCl_4$ suggesting the Ti:**26** complex is exceptionally stable. If the less reactive crotonate **26** (R=Me) dienophiles are used, the reaction proceeds smoothly whereas for other auxiliaries polymerisation is the major reaction. In addition, a (*S*)-configuration equivalent is also available. (*S*)-*N*-Methyl-2-hydroxysuccinimide **28** readily available from (*S*)-malic acid displays properties similar to that of (*R*)-pantolactone but induces selectivity of opposite configuration.[23] There are many examples of the use of pantolactone in synthesis,[24] including the formation of prostaglandin precursor (1*S*)-**15b** in 79% yield and 94% d.e.



Scheme 13

1.4c Auxiliaries based on naturally occurring alcohols.

Other auxiliaries have been developed which are based on naturally occurring alcohols. The acrylate of the monobenzoate **31** derived from the cheap and readily available isosorbide readily undergoes Lewis acid catalysed Diels-Alder reaction. Using $SnCl_4$ reaction with cyclopentadiene gives the (*S*)-*endo* product in 96:4 d.r. In contrast the acrylate of the closely related epimeric isomannide **32** gives the (*R*)-*endo* adduct in 95:5 d.r. with $EtAlCl_2$ as the Lewis acid.[25]



Scheme 14

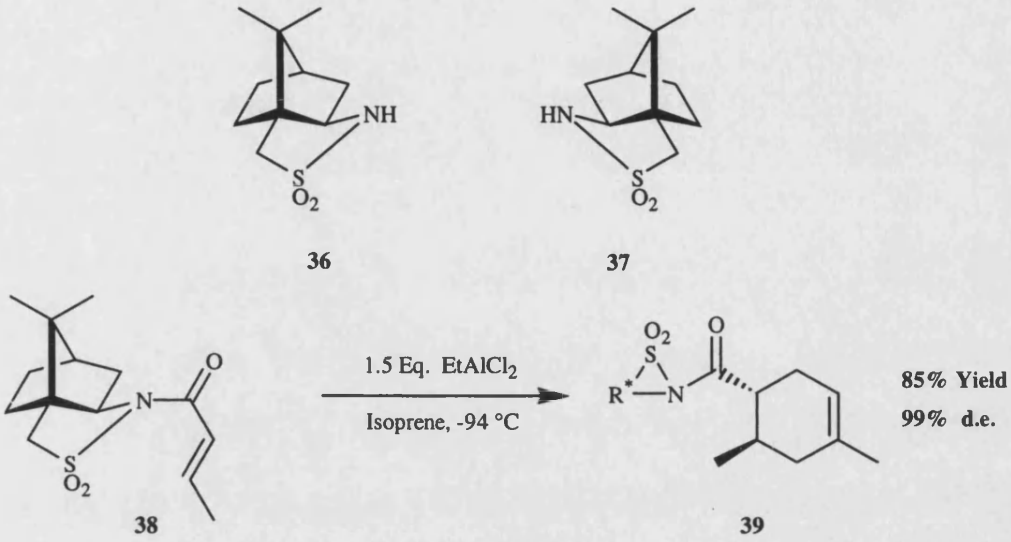
The $TiCl_4$ or $SnCl_4$ mediated Diels-Alder reaction of cyclopentadiene and chiral acryloyl esters derived from chiral cyclitols **33** proceed with excellent diastereoselectivity (up to 99:1) in ether *via re*-face attack. In contrast, changing the solvent to toluene or hexane affords the cycloadducts derived from *si*-face attack. In non-coordinating solvents, the Lewis acid binds to both the acrylate carbonyl oxygen and the benzylic ether oxygen forcing the intermediate to adopt a conformation where the *re*-face is blocked.[26] The acrylates derived from the chiral spiro-fused diol **34** react with cyclopentadiene to give the *endo*-adduct in >99% d.e. using BCl_3 as the Lewis acid.[27] Unfortunately it is difficult to hydrolyse the bicycloester in the presence of the pivalate with iodolactonisation being the only method whereby the auxiliary could be recovered. By changing to the pivalamide **35**, selective hydrolysis can be achieved under basic conditions.[28]

1.5 Auxiliaries based on amides

1.5a Camphor and camphor lactam based auxiliaries

Some of the most useful chiral auxiliaries are the bornane-10,2-sultam derivatives **36** and **37**, available from (+)- and (-)-camphor-10-sulfonyl chlorides.[17] Initially

conceived as auxiliaries that will electronically enhance the dienophilicity of their derivatives, both acryloyl sultam and crotonoyl sultam **38** add to a range of dienes in the presence of either $EtAlCl_2$ or $TiCl_4$ with high diastereoselectivity.

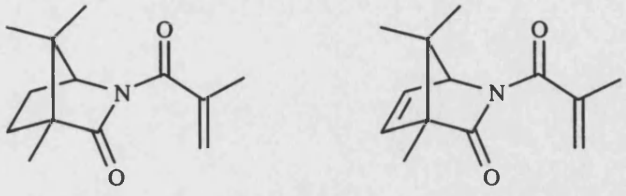


Scheme 15

Adducts are formed in high yield and can be obtained virtually diastereomerically pure after crystallisation. The observed stereocontrol is consistent with a model whereby chelation occurs between the SO_2 and carbonyl groups which directs the diene to the less hindered C_α-*re*-face. Reduction of the cycloadducts with $LiAlH_4$ generates the pure alcohols and refurnished the sultam. Alternatively the adducts can be saponified with LiOH to yield the carboxylic acid without epimerisation. In another method,[29] sultams can be cleaved by heating with allyl alcohol and $Ti(O^iPr)_4$ to yield the recovered sultams and allyl esters. These esters can then be hydrolysed with Wilkinsons catalyst to give the enantiomerically pure carboxylic acids. This method has the advantage that it is compatible with base sensitive substrates. By using the alternative auxiliary **37** the sense of asymmetric induction can be reversed. Reactions of the *N*-methacryloylsultams derived from auxiliary **36** show poor selectivity in the

Diels-Alder reactions, however this can be improved by altering the substituents attached to the sultam auxiliary.[30]

Alternatively, camphor lactams have been extensively studied for the effect of structural variations on the selectivity of the Diels-Alder reactions of their methacrylates.[31]



40 **41**

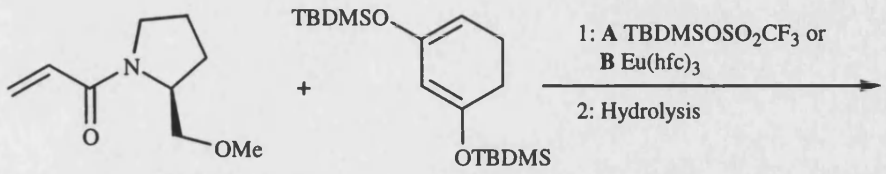
Scheme 16

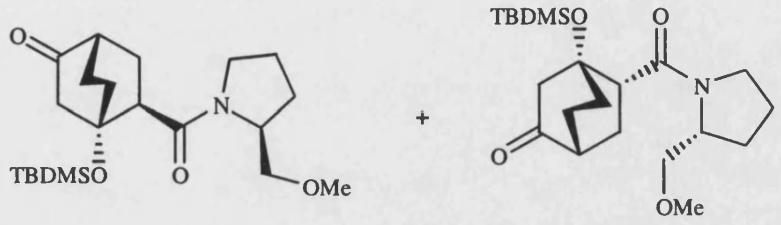
In the $MeAlCl_2$ catalysed Diels-Alder reaction of cyclopentadiene and the camphor lactam derivative **40** the cycloadducts were isolated in 91:9 *endo:exo* selectivity and 82% d.e. for the *endo* isomer. It was anticipated that removal of the *endo*-hydrogens of the ethane bridge would increase the selectivity. In fact, when camphor lactam derivative **41** is reacted under identical conditions the *endo:exo* selectivity drops to 1.8:1 and 55% d.e. Although this modification was unsuccessful, further modifications may produce a highly selective auxiliary.

1.5b Auxiliaries based on amino acids.

Amino acids are naturally occurring compounds that have been utilised as starting materials for various chiral auxiliaries.[32] The widely used RMP auxiliary,[33] synthesised by Enders, has also been used as a chiral auxiliary in the Diels-Alder reaction.[34] The Lewis acid catalysed Diels-Alder reaction of 1,3-disiloxycyclohexadiene with the RMP-acrylamide **42** followed by mild hydrolysis of

the primary adducts proceeded smoothly although the *endo*:*exo* ratio was strongly controlled by choice of the catalyst.



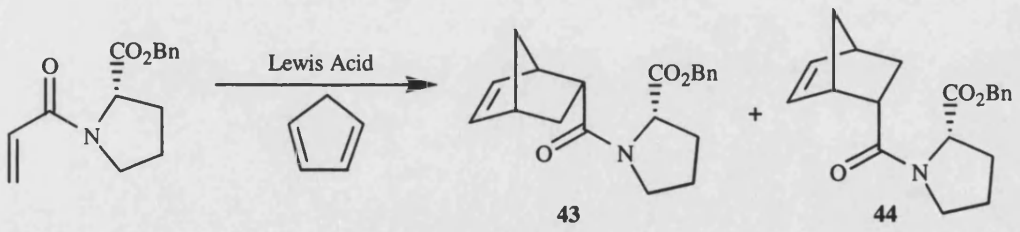


EXO ***ENDO***

A	*endo*:*exo* = 84:16, d.e.$_{endo}$ = 77%, d.e.$_{exo}$ = 96%
B	*endo*:*exo* = 0:100, d.e.$_{endo}$ = NA%, d.e.$_{exo}$ = 25%

Scheme 17

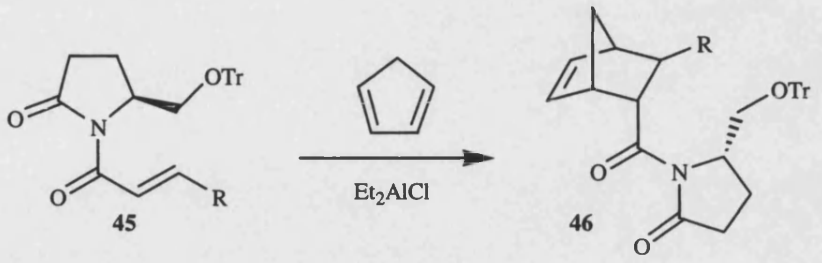
(*S*)-Proline benzyl esters have also been examined.[35] Again, by changing the catalyst the diastereoselectivity of the product can be reversed ($TiCl_4$; **43**:**44** 97:3 *vs.* $EtAlCl_2$; **43**:**44** 10:90) in a similar manner to the reactions of pantalactone derivatives. Again competition between different coordination compounds for tetravalent Lewis acids accounts for this observation.



Scheme 18

(*S*)-5-(Trityloxymethyl)pyrrolidin-2-one [36] is unique in that the trityloxymethyl group adopts an axial conformation, probably due to interactions between the lone pair of the ether oxygen and the antibonding orbital of the O-C σ bond of the ring. The imides **45**

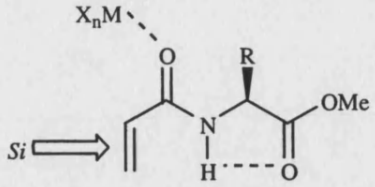
are good dienophiles reacting for instance with cyclopentadiene to give the cycloadduct with good *endo*-approach (>99%) and very high diastereoselection (up to 99%) in the presence of Lewis acids.[37] The adducts can be cleaved by treatment with $LiOCH_2Ph$ to form the benzyl ester and the recovered auxiliary.



Scheme 19

Other pyroglutamic acid derivatives can be used again giving good selectivity if Et_2AlCl is used as a Lewis acid in toluene.[38] Both enantiomers of 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone have been examined in a variety of Diels-Alder reactions.[39] Their acrylates react with good selectivity with a range of dienes, however other derivatives show worse results.

In comparison to proline, auxiliaries based on phenylalanine and alanine show results which do not correspond to the models proposed by Helmchen to explain the stereochemistry of the reaction between lactate acrylates and cyclopentadiene.[40] When the amino acids contain an NH group, the participation of an intermediate with an intramolecular hydrogen bond must be considered. Attack of cyclopentadiene occurs preferentially on the *si*-face of the dienophile. Selectivity is better for phenylalanine, **47** R=Bn (*endo*:*exo* = 20.4:1, 64% d.e.) than alanine **47** R=Me (*endo*:*exo* = 8.4:1, 30% d.e.) due to increased steric effects.

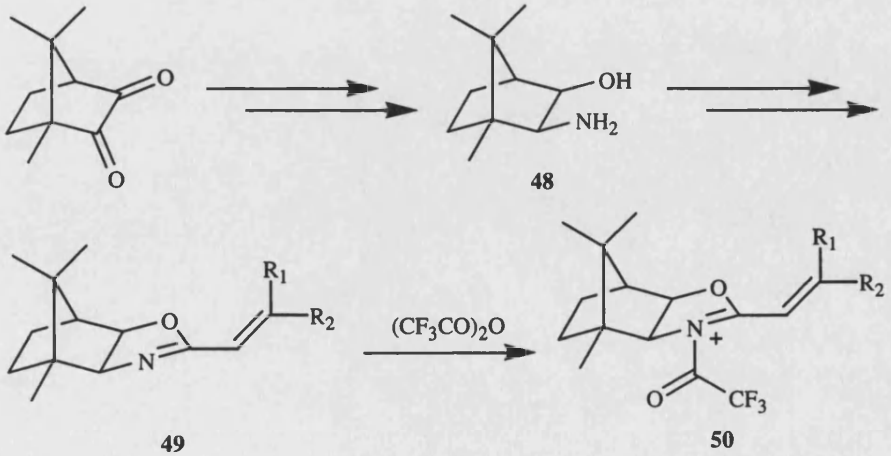


47

Scheme 20

1.5c Amino alcohol based auxiliaries

Several auxiliaries based on 1,2-amino alcohols have been developed.[41] The most successful oxazoline auxiliaries are those based on camphor.[42] α,β-Unsaturated camphor oxazolines are derived from camphorquinone by initial transformation to the amino alcohol **48**. *N*-Acylation with an α,β-unsaturated acid chloride and subsequent cyclisation with phosphorus oxychloride yields the desired substrate **49**. In contrast to many Diels-Alder reactions, these are activated by addition of trifluoroacetic anhydride. This provides the imino ether salt **50** which acts as an activating group allowing the reaction to proceed at low temperature. High diastereofacial control occurs as the camphor unit directs attack to the α-face of the dienophile and steric hindrance between the methyl group of the camphor and the acyl group on nitrogen forces the ethylenic side chain to adopt the s-*trans* conformer.



Scheme 21

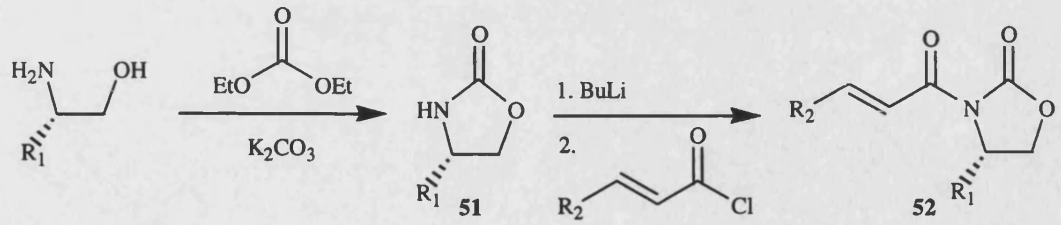
Table 1: Diels-Alder reactions of α,β-unsaturated oxazolines

R_1	R_2	Diene	Temp °C (time)	Yield %, (*endo* %)	Degree of selectivity
H	Me	Cyclopentadiene	-78 (4 h)	76 (100)	94
H	H	Cyclopentadiene	-78 (4 min)	70 (100)	>99
H	H	Cyclohexadiene	-15 (30 min)	82 (100)	>99

Generally the oxazoline group is hydrolysed using strongly acidic conditions. However, for certain substrates where this methodology fails the oxazoline adducts can be treated with benzyl chloroformate in the presence of sodium carbonate affording the corresponding carbamates. These can in turn be hydrolysed to the starting amino alcohol and the desired carboxylic acid in good yield.

1.5d Oxazolidinone auxiliaries [43]

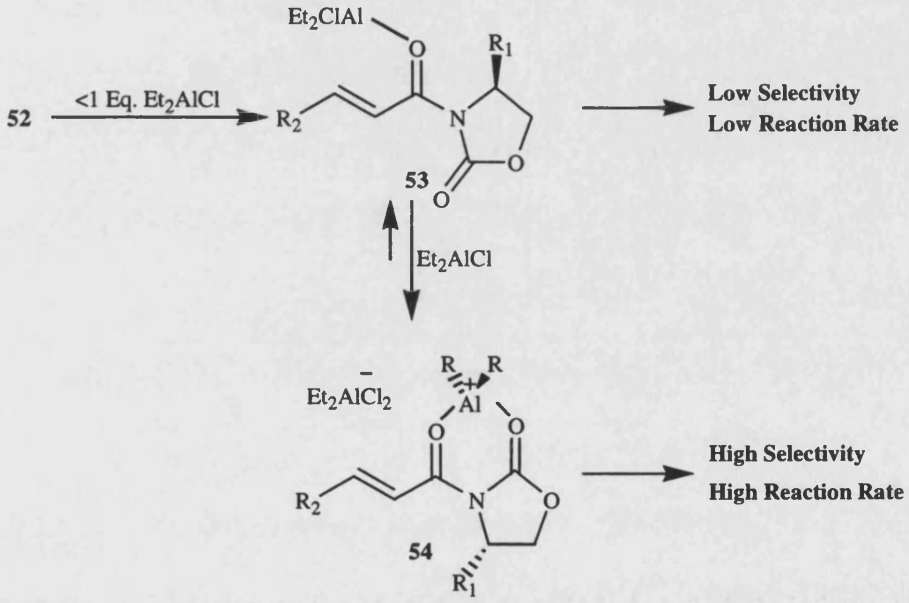
Possibly the most widely used chiral auxiliaries in organic synthesis today are those based on oxazolidinones **51**.[44] Initially developed as auxiliaries for enolate chemistry,[45] oxazolidinones are readily available from amino alcohols *via* a simple cyclisation reaction with diethyl carbonate. Dienophiles **52** are equally easily prepared from the lithiated oxazolidinone and the requisite acid chloride. Unlike 8-phenylmenthol derivatives **14**, the oxazolidinone substrates are usually crystalline and have excellent shelf lives once obtained in a pure state.



Scheme 22

An extensive study on the effect of different Lewis acids showed that more than one equivalent of diethylaluminium chloride promoted the most diastereoselective Diels-

Alder reaction.[46] When less than one equivalent is used, both the rate of reaction and diastereoselectivity are reduced. It is presumed that a slow reaction occurs from one of several possible conformations of 1:1 complex **53**, leading to a mixture of diastereomers. In the presence of excess Lewis acid, chloride ionisation of complex **53** occurs to give the cationic species **54**, which is highly ordered and reactive. In accordance with this diene attack occurs from the less sterically hindered C_α-*si* face of the dienophile. Enantioselectivity arises due to favoured formation of the s-*cis* conformer, again due to steric hindrance caused by the oxazolidinone substituent.



Scheme 23

The power of oxazolidinones as chiral auxiliaries is shown in the vast number of Diels-Alder reactions that they can control and even combinations of unreactive dienes and dienophiles proceed smoothly and with high selectivity (**Table 2**). It should also be noted that oxazolidinones that are psuedo-enantiomers can be obtained. Those derived from (*S*)-valine (**52**, R_1= Me_2CH) and those derived from norephedrine give complementary results (**Entries 1 and 2**). Best selectivities are given when oxazolidinones derived from phenylalaninol (**52**, R_1= CH_2Ph) are utilised. In an analogous manner to that already mentioned for the increased selectivity of 8-

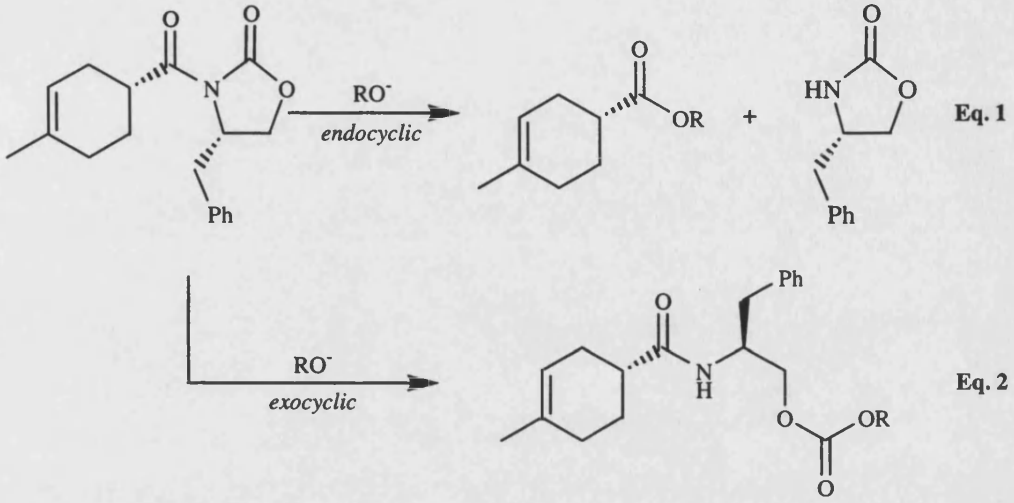
phenylmenthol over menthol, π-stacking effects are important. This enhanced steric effect, promoted by van der Waals attractions, further stabilises the transition state **54** leading to an enhancement in the diastereoselectivity of the reaction. In a recent development,[47] (*R*)-4-diphenylmethyl-2-oxazolidinone (**52**, R= $CHPh_2$) has been shown to enhance this π-stacking effect. In addition, derivatives of oxazolidinone **52** can also undergo hetero Diels-Alder reactions [48] and suitable triene derivatives undergo highly selective intramolecular Diels-Alder reactions.

Table 2: Diels-Alder Reactions of **52**.

R_1	R_2	Diene	*endo:exo*	*endo* d.s.	Yield %
$CHMe_2$	H	cyclopentadiene	>100:1	93:7	81
Norephedrine	H	cyclopentadiene	100:1	5:95	82
CH_2Ph	H	cyclopentadiene	>100:1	95:5	78
CH_2Ph	Me	isoprene	-	94:6	83
$CHPh_2$	Me	isoprene	-	>99%d.e.	86
$CHMe_2$	Ph	cyclopentadiene	No *exo* observed	93:7	83

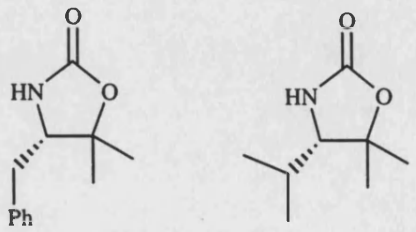
Unlike other auxiliaries, mild and selective techniques exist for the non-destructive removal of oxazolidinones without attendant racemisation of the newly created stereocentres. Methods have been described for auxiliary removal *via* transesterification (LiOBn,[48] $Ti(OBn)_4$,[49]) hydrolysis (LiOH),[49] and reduction ($LiBH_4$).[50] The site of nucleophilic cleavage of *N*-acyloxazolidinones is subject to both steric and electronic factors. In the absence of significant steric hindrance in the vicinity of the exocyclic carbonyl group, electronic factors direct hydrolysis in the desired manner to afford the carboxylic acid and recovered chiral auxiliary (**Eq. 1**). However, as the steric requirements of the exocyclic substituents are increased, competition from the undesired reaction involving attack at the endocyclic auxiliary carbonyl group is observed (**Eq. 2**). However by simply changing the attacking nucleophile from that of alkoxide to peroxide even the most sterically demanding

substrates can be cleaved successfully.[51] In all cases, isolated yields of the desired products and re-isolated oxazolidinones are high.



Scheme 24

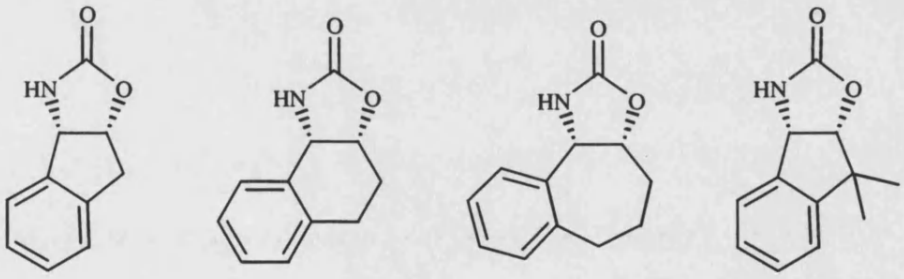
One of the great advantages in using oxazolidinone auxiliaries is their ability to be recycled. This is especially true during large-scale synthesis as the auxiliaries are expensive. However on a large scale cleavage techniques which utilise peroxide can become hazardous. Various auxiliaries have been developed which circumvent this problem. The so-called "*superquat*" auxiliaries **55** and **56** contain geminal dimethyl groups at C5 which completely suppress the endocyclic cleavage pathway and also convey a high degree of crystallinity to both the auxiliaries and their acylated derivatives, enabling simple purification by recrystalisation.[52] These auxiliaries are cleaved in good yield by simple LiOH hydrolysis.[53]



55 **56**

Scheme 25

Other amino alcohols have been utilised as starting materials for oxazolidinone auxiliaries. Oxazolidinones based on phenyl glycinol are known to show poor diastereoselectivity in the Diels-Alder reaction (35% d.e.). Amino indanol is a constrained analogue whose oxazolidinones **57** show high selectivity (>88% d.e.).[54] Analogues with different ring sizes (**58** and **59**) again show low levels of selectivity (30-35% d.e.). Molecular modelling studies show that auxiliaries **58** and **59** are conformationally flexible whereas the amino indanol derived auxiliary **57** is essentially rigid. Furthermore the cycloadducts are easily cleaved with LiOBn which allows easy recovery of the auxiliary. Another analogue of amino indanol containing geminal dimethyl groups can also be synthesised, however resolution with mandelic acid is required.[55] Diels-Alder reactions of acrylates and crotonates of oxazolidinone **60** catalysed by Et_2AlCl give the desired cycloadducts in high selectivity (>90% d.e.).[56]

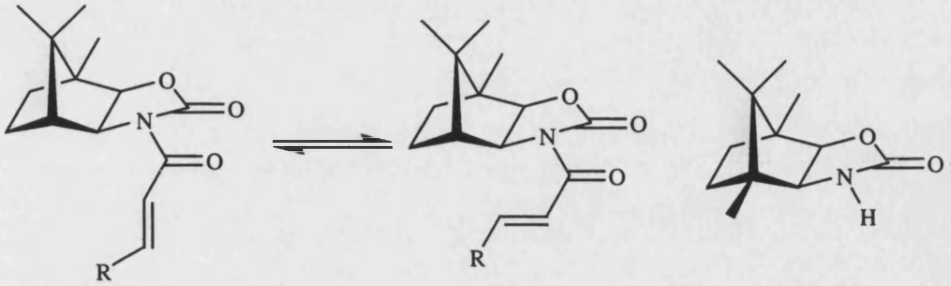


57 **58** **59** **60**

Scheme 26

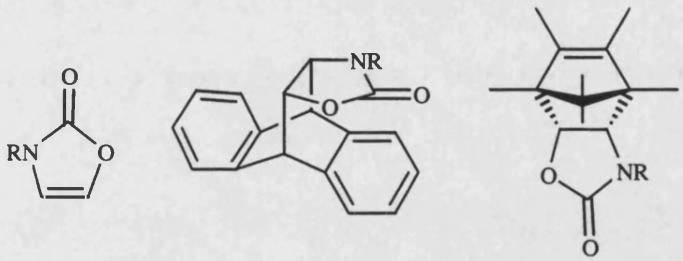
Oxazolidinones based on camphor have also been utilised.[57] Initial attempts were disappointing due to insufficient π-topological bias imparted by the auxiliary when bearing *N*-acryloyl substituents such as *N*-acyl derivative **61**. The origin of the poor stereoselection arises from the free rotation of the carbonyl C_α bond in the *N*-acryloyl moiety of the dienophile which allows attack by the diene on both enantiofaces *i.e.* the dienophile can react in either the S-*trans* or S-*cis* conformation. By changing the

auxiliary to oxazolidinone **62** good stereoselectivity can be achieved (>99% d.e. *vs.* 60% d.e. for **61**).



Scheme 27

The unsaturated oxazolidinone **63** undergoes an uncatalysed Diels-Alder reaction with a range of dienes to give conformationally fixed bi- and tricyclic chiral auxiliaries.[58] The Et_2AlCl catalysed Diels-Alder reaction of the crotonates of oxazolidinones **64** and **65** and cyclopentadiene give cycloadducts with very high selectivity (**64**: *Endo:Exo* = 49:1, 96% d.e.; **65**: *Endo:Exo* = 99:1, 99% d.e.). Unfortunately, these adducts need to be separated from their enantiomers before use, limiting their accessibility as universal chiral auxiliaries.

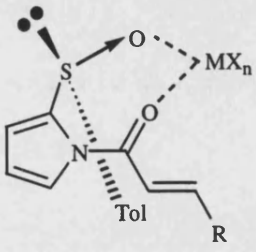


63 **64** **65**

Scheme 28

1.6 Sulfinyl based auxiliaries

Another class of auxiliaries is based on sulfur compounds. Initial attempts showed poor selectivity and low reactivity.[59] This can be improved by adding extra activating groups to the dienophile, although this somewhat defeats the object of using a chiral auxiliary. In addition most auxiliaries require prior oxidation to the sulfone before removal inhibiting its ability to be recovered. By making the chiral sulfoxide group remote this limitation can be overcome.[60] The pyrrole sulfoxide **66**, easily obtained from the enantiomerically pure (1*R*, 2*S*, 5*R*, S_S)-menthyl toluene-*p*-sulfinate, can be converted into the corresponding α,β-unsaturated compound by treatment with the corresponding acid chloride. The use of $BF_3.Et_2O$ or $ZnCl_2$ gives poor selectivity, however by utilising either $AlCl_3$ or $Yb(OTf)_3$, good selectivity can be achieved. Use of a suitable coordinating metal forms a stable metal chelated structure where attack of the diene occurs on the opposite face to the more bulky tolyl ligand. The auxiliary can be easily removed by treatment with lithium alkoxide to give the ester in high yield accompanied by efficient removal of the sulfinyl pyrrole.



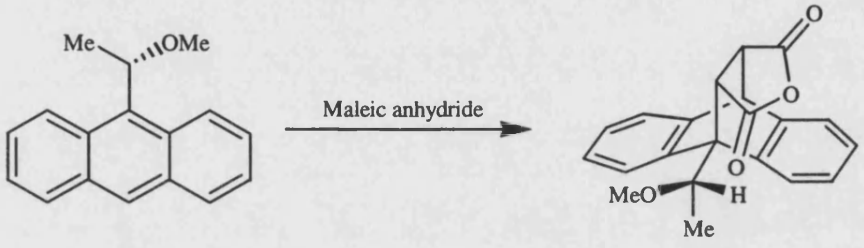
66

Scheme 29

1.7 New classes of auxiliaries

All auxiliaries discussed thus far are limited in the type of transformations they can undergo due to the nature of the attachment at the acyl carbon. Development of a

different attachment/cleavage strategy would allow a number of transformations to occur on the derived cycloadduct that are incompatible with most commonly used auxiliaries and as such a photoactivated chiral auxiliary is currently under development.[61] An enantiomerically pure derivative of anthracene is easily prepared in three steps. Photoinduced Diels-Alder reaction of anthracene **67** with maleic anhydride proceeds in good yield to form a single diastereomer of cycloadduct **68**. It is hoped that this substrate can undergo further reactions before flash vapour pyrolysis induced retro Diels-Alder reaction allows recovery of the original anthracene. If this work is successful a useful class of auxiliaries will have been developed.



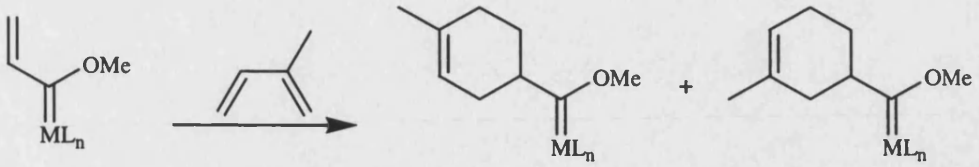
67 **68**

Scheme 30

1.8 Transition Metal based Chiral Auxiliaries

1.8a Carbene type auxiliaries

Fisher type carbene complexes such as **69** have been utilised as dienophiles in the Diels-Alder reaction.[62] The resonance structures of carbene complexes show the same type of polarisation commonly associated with esters, the closest carbon analogue of Fisher carbene complexes. It has been established that α,β-unsaturated carbenes can act as dienophiles with rates, stereo-and regioselectivity comparable to that for Lewis acid catalysed reactions.[63]



69 **70** **71**

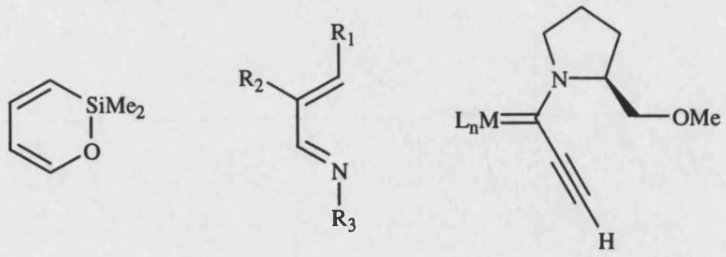
Scheme 31

Table 3: Diels-Alder reactions of carbene complexes

ML_n	Catalyst	Time	Yield %	70/71
O	-	7 Months	54	70:30
O	$AlCl_3$	3 h	50	95:5
$Cr(CO)_5$	-	3 h	70	92:8
$Mo(CO)_5$	-	1 h	61	94:6
$W(CO)_5$	-	2 h	87	91:9

In addition to isoprene, carbene complexes react with a wide range of dienes with rates that can be as much as $2x10^4$ faster than their organic analogues. One advantage of carbene complexes as dienophiles are the mild reaction conditions that can be used. Thermal or Lewis acid catalysed reactions utilising diene **72** results in decomposition of the product cycloadducts under the reaction conditions. However, by utilising carbene complexes, the reactions can be made to proceed smoothly.

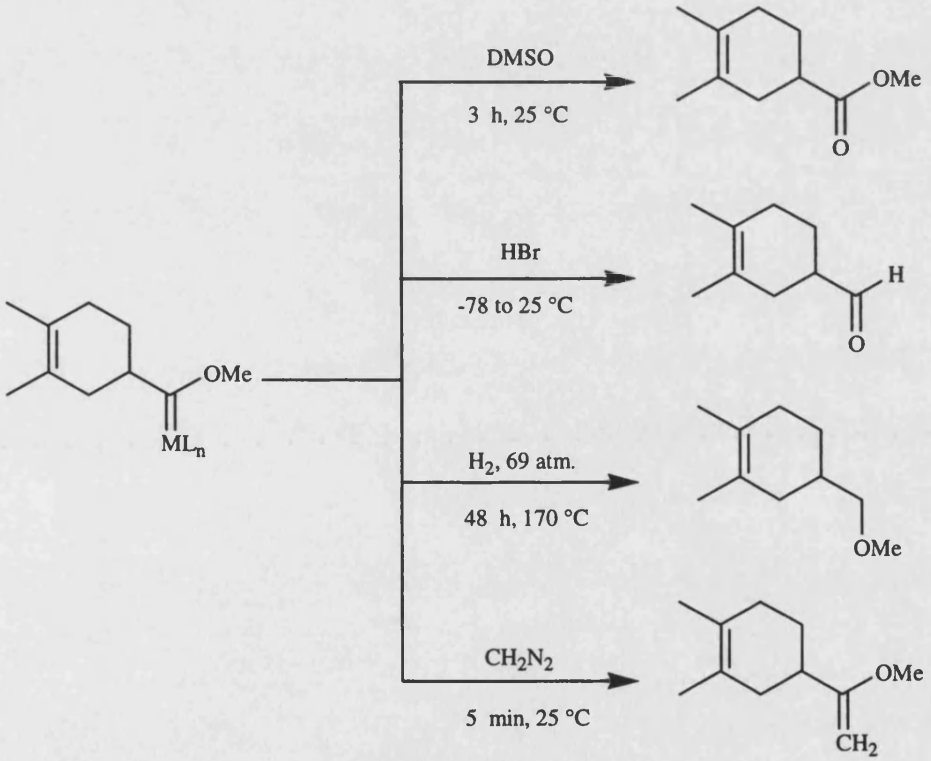
Heterodienes such as diene **73** have also been used in the synthesis of dihydropyridines.[64] Reactions of acetylene carbenes containing enantiomerically pure pyrrolidine ligands **74** give products in good yield and up to 70% d.e. although reactions are very slow (2-3 days).[65]



72 73 74

Scheme 32

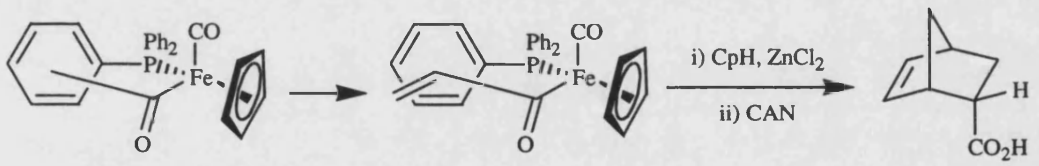
In addition to their high selectivity and tolerance of organic functionality, carbene complexes are easy to prepare and handle. There also exists a wide range of cleavage techniques for the conversion of the carbene into a variety of organic functional groups.



Scheme 33

1.8b Iron acyls as chiral auxiliaries

Like carbon atoms, metals atoms can be chiral centres. Both enantiomers of the iron acyl complex **75** are commercially available and have been utilised extensively as chiral auxiliaries in a range of reactions.[66] These iron acyls can easily be transformed into the enantiomerically pure acryloyl and crotonoyl complexes.[67] Diels-Alder reaction of the acrylate **76** followed by oxidative removal of the iron acyl group with CAN gave predominantly (2*S*)-(-)-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid **77** *via* reaction of the face of the dienophile opposite to the triphenylphosphine ligand.[68] Conversion of carboxylic acid **77** into the corresponding iodolactone showed the product to have >95% e.e. These reactions appear to be useful, but thus far have not been explored in great detail.



75 **76** **77**

Scheme 34

1.9 Conclusions

From the range of different chiral auxiliaries discussed in this introduction some general design features of the "perfect" chiral auxiliary can be proposed.

- A chiral auxiliary must be readily available in enantiomerically pure form. Ideally both enantiomers should also be easily accessible.
- It must be simply attached to the required functional group with no loss of enantiomeric excess.
- It must induce highly stereoselective reactions and preferably impart crystallinity to all intermediates to facilitate easy purification of the product diastereomer.
- The auxiliary must be easily removed and recycled, again without compromising the stereochemical integrity of the product fragment.

In addition, there are some limitations to the use of chiral auxiliaries.

- Each use of a chiral auxiliary adds two steps to the overall synthetic scheme.
- The auxiliary must be used in stoichiometric amounts as it needs to be bound covalently to the substrate throughout the reaction where stereocontrol is required.
- Being enantiomerically pure compounds, chiral auxiliaries are generally expensive.

To improve the overall appeal of the use of chiral auxiliaries in organic synthesis it would be advantageous if methodology could be developed whereby chiral auxiliaries can be used in a catalytic manner.

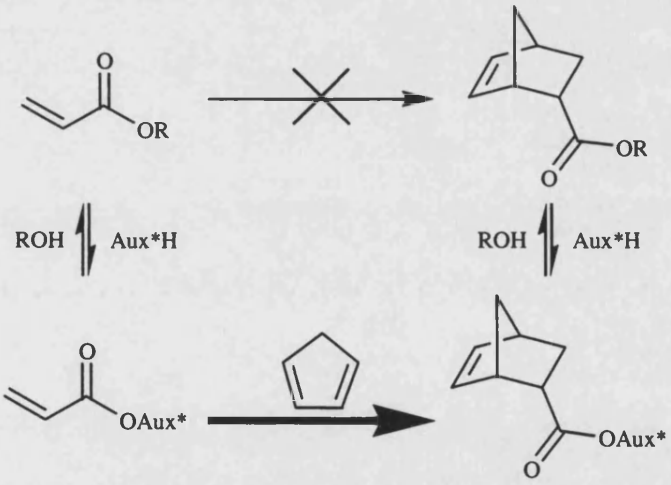
Chapter 2

Auxiliary Accelerated Diels-Alder Reactions

2) Auxiliary Accelerated Diels-Alder Reactions

2.1 Catalytic Chiral Auxiliaries

As has been shown in the introduction, the use of enantiomerically pure auxiliaries in asymmetric synthesis to control the stereochemical outcome of reactions, although of fundamental importance and of widespread usage in synthesis, suffers from important drawbacks in terms of synthetic efficiency. In order to try to overcome these deficiencies it is envisaged that chiral auxiliaries can be used in a catalytic manner whereby the attachment and detachment of the auxiliary would occur in one pot *via* a reversible reaction such as transesterification. A generalised catalytic cycle is shown in **Scheme 35**, using the Diels-Alder reaction as a model. It should be noted that this kind of catalytic cycle could, in principle, be applied to many other reactions.



Scheme 35

In order for the above catalytic cycle to function successfully, three major criteria which needed to be satisfied, were identified:

a) The catalytic auxiliary bound substrate should react more quickly than the unbound substrate when both are present in the reaction mixture. If this were not the case, the

achiral substrate would react competitively, significantly lowering the level of asymmetric induction.

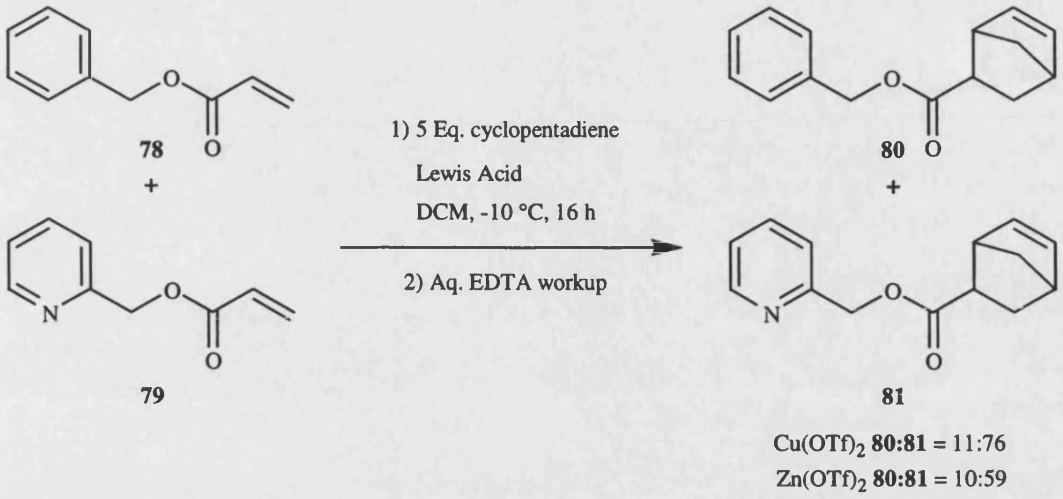
b) Attachment of the auxiliary must be reversible under the reaction conditions to allow catalytic use of the auxiliary.

c) The auxiliary bound cycloaddition must be highly stereoselective.

As has been shown previously, a wide range of chiral auxiliaries can be utilised in the Diels-Alder reaction to impart a high degree of stereocontrol and therefore at this juncture, methods for obtaining good rate differences between the Diels-Alder reactions of the starting and auxiliary bound substrates were examined.

2.2 Acceleration *via* coordination effects

One approach that could be utilised to obtain a good rate difference between the two substrates would be to accelerate the rate of reaction for the auxiliary bound substrate. Previous work within the group [69] has shown that incorporation of a suitable donor atom, such as in the 2-pyridyl group, would allow a suitable Lewis acid species to be bound and accelerate the rate of reaction at the double bond *via* chelation. Competition experiments between equimolar quantities of benzyl propenoate **78** and (2-pyridyl)methyl propenoate **79** in the presence of various Lewis acids were carried out using cyclopentadiene as the diene. Copper(II) and zinc(II) triflate both accelerate the Diels-Alder reaction for the (2-pyridyl)methyl substrate but have virtually no effect on the benzyl substrate demonstrating that the auxiliary is able to modify the rate of reaction.



Scheme 36

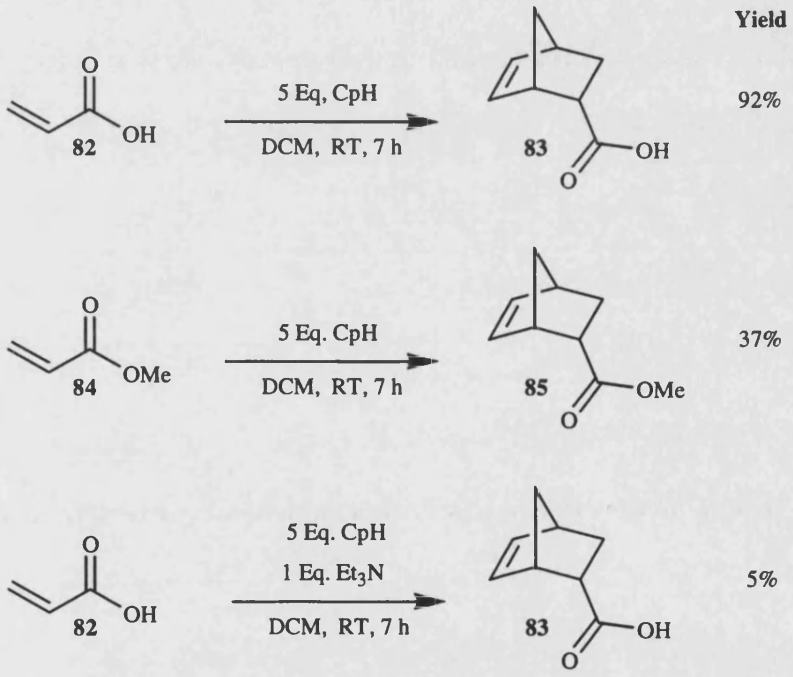
Recent work by Shipman [70] has shown that Et_2AlCl can selectively bind to the 2-hydroxyethyl ester group in the presence of ethyl and 2-methoxyethyl ester functionalities. This also leads to a selective increase in the rate of Diels-Alder reaction for these substrates *via* chelation, in an analogous manner to that for pyridyl esters.

Although the principle of Lewis acid promoted rate enhancement of auxiliary bound substrates containing nitrogen or oxygen donor atoms in the presence of substrates containing no such donor atom in competition experiments was demonstrated with a fair degree of success, rate discrimination levels were not high enough to apply the pyridyl group as a potential catalytic chiral auxiliary. One fundamental problem is the low reactivity of both substrates at the same rate in absence of Lewis acid promoter, contributing a significant background rate of non-discriminatory cycloaddition. To try to overcome this problem, electronic effects on the rate of Diels-Alder reaction were examined.

2.3 Electronic effects on the Diels-Alder reaction

The LUMO of a dienophile and hence its reactivity depends upon the nature of the electron withdrawing group attached to the dienophile.[2a], [71] By changing to a worse electron withdrawing group the dieneophile becomes less reactive. By controlling the electronic properties of the dieneophile, it should be possible to control the reactivity of the substrates. As such, the starting substrate can be deactivated relative to the auxiliary bound substrate.

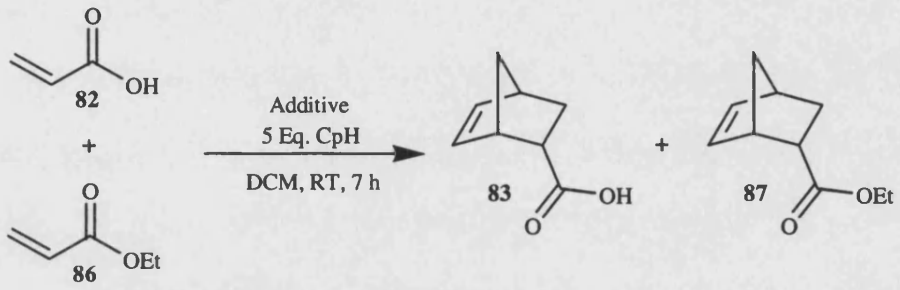
It was envisaged that formation of a carboxylate from a carboxylic acid would render the substrate a worse dieneophile. This was investigated as shown in **Scheme 37**.[72]



Scheme 37

These results show a remarkable difference in reactivity with acrylic acid **82** reacting much faster than the corresponding acrylate ester **84**, which in turn is more reactive than the carboxylate (relative ratios 19:8:1). The effects of certain additives on the relative rates of Diels-Alder reaction were examined (**Table 4**).[72] As was expected, when no additive is used, the acid product **83** predominates. By using a suitable base

the selectivity can be reversed. Utilising DBU instead of triethylamine gives a remarkable increase in selectivity. This can be explained by assuming that the proton in the trialkylammonium cation is more readily available to form a hydrogen bond with the acrylate than in the stronger base DBU, resulting in acceleration of both reactions *via* "normal" proton catalysis. In the tetrabutylammonium case no proton is present resulting in the high selectivity. Addition of a catalytic amount of trifluoroacetic acid decreases the selectivity again *via* activation of both reaction partners by "normal" proton catalysis.



Scheme 38

Table 4: Effect of additives on competitive Diels-Alder reactions.

Additive	Ratio 83:87
None	1:0.5
1.05 Eq. Et_3N	1:14
1.05 Eq. DBU	1:167
NBu_4^{+} [a]	1:70
0.1 Eq. CF_3CO_2H	1:0.7

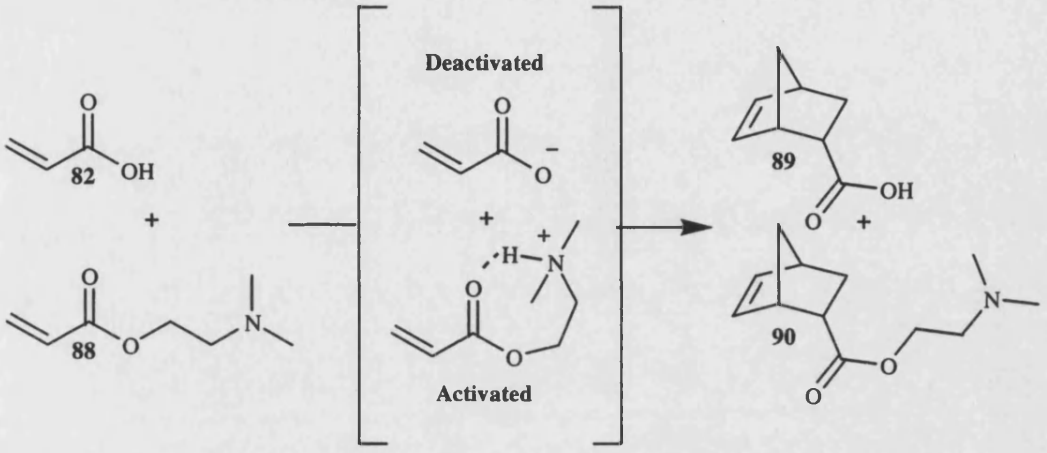
[a]: Reaction run using preformed tetrabutylammonium salt.

Solvent is known to have an effect on the rates of Diels-Alder reactions.[9], [73] By re-running competition reactions with 1.05 Eq. triethylamine as the additive, DCM and methanol were found to give the highest selectivity.

2.4 Combination of electronic and coordinative effects

With these results in hand, attempts were made to further enhance the selectivity by combining electronic and coordination effects. If 2-(dimethylamino)ethyl acrylate **88**

containing a suitable donor atom is mixed with acrylic acid **82** the donor atom should deprotonate the acid. The *in situ* formation of the carboxylate will deactivate the acid towards reaction. In addition, the ester functionality will be activated towards reaction by formation of a Lewis acid interaction between the newly protonated auxiliary donor atom and the carbonyl group, in a similar way to the activation of pyridyl esters by Lewis acids. This should result in a favourable difference in rate between the acid and ester substrates.



Scheme 39

The relative rates of reaction for acrylic acid **82**, amino ester **88** and competition reactions between mixtures of both substrates were determined by GC analysis after calibration with known standards. The data, shown in **Appendix 1**, allow rate curves (**Figures 1** to **3**) to be plotted. As cyclopentadiene was added in large excess (5 Eq.), and therefore its concentration will remain relatively unchanged throughout the reaction it is possible to assume a psuedo-first order rate equation. The rate constant for the reaction can be determined by **Equation 1**.

$$[SM]_t = [SM]_0 e^{-kt}$$

$$\Rightarrow -(\ln [SM]_t / [SM]_0) = kt$$

Equation 1

Therefore by plotting the required graph, determination of the gradient allows the rate constant to be found. This in turn allows the relative rates of reaction to be calculated.

Table 5: Relative rates for various competition reactions

Reaction Type	Substrate	Relative Rate
Independent	**82**	1000
Independent	**88**	114
1:1 Mixture **82:88**	**82**	40
1:1 Mixture **82:88**	**88**	235
1:2 Mixture **82:88**	**82**	13
1:2 Mixture **82:88**	**88**	141

As was expected, acrylic acid **82** reacts 8 times more quickly than amino ester **88**. When mixed in a 1:1 ratio the selectivity is reversed with the amino ester **88** now reacting 6 times more quickly. In a 1:2 mixture, the trend is the same but now the amino ester **88** reacts 11 times more quickly. In both cases the reaction of acrylic acid **82** has been retarded considerably compared to when no auxiliary is present. This suggests it has been deprotonated to yield the electronically deactivated carboxylate. Likewise the amino ester **88** reaction proceeds approximately 2 times faster. This suggests that the protonated form of the auxiliary is acting as a Lewis acid and so accelerates the reaction.

These results suggest that it is possible to obtain a good rate difference between activated and deactivated substrates and therefore the reversible formation of esters from carboxylates was examined.

Figure 1: Independent Reactions for formation of **89** vs **90**.

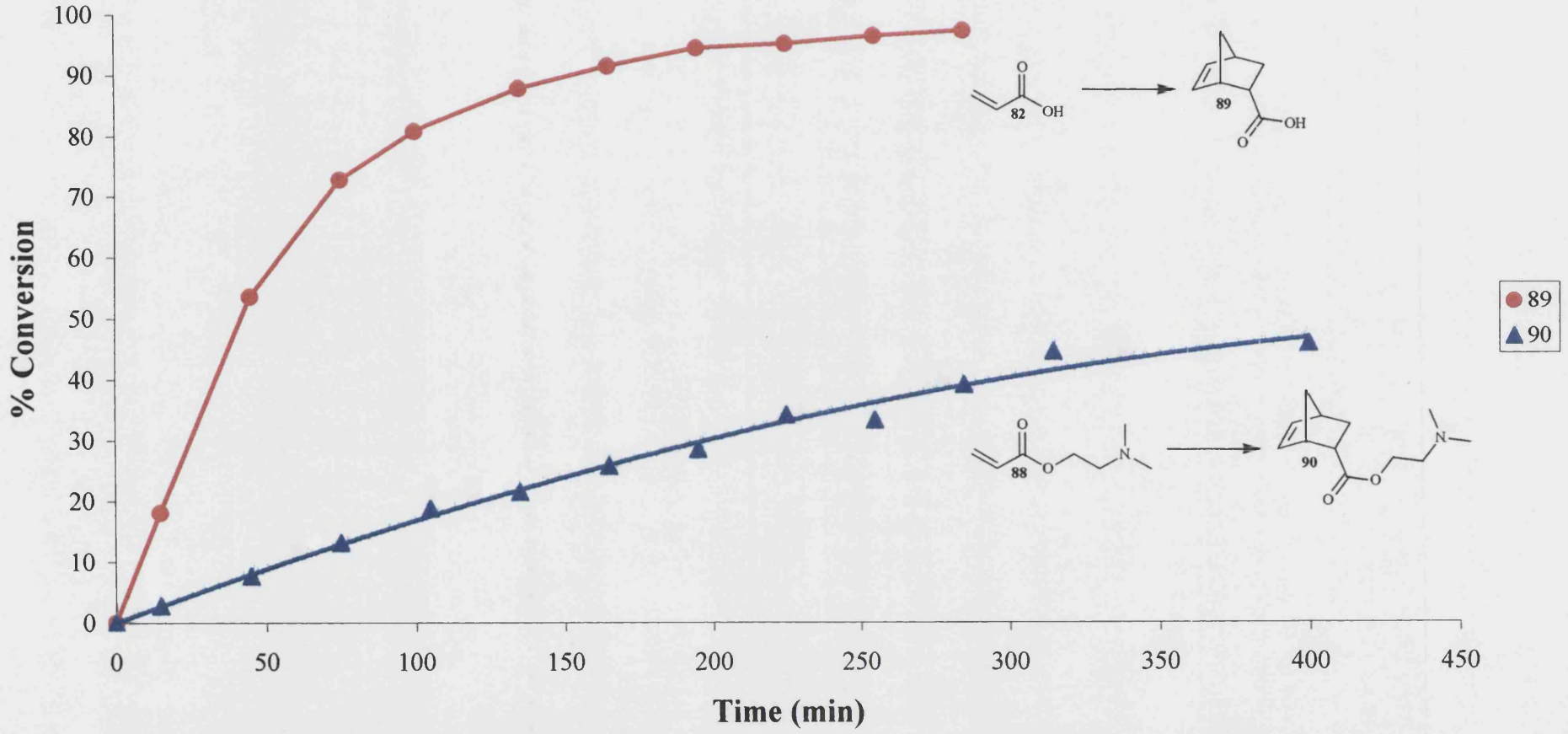


Figure 2: 1:1 Competition Reaction for formation of **89** vs **90**.

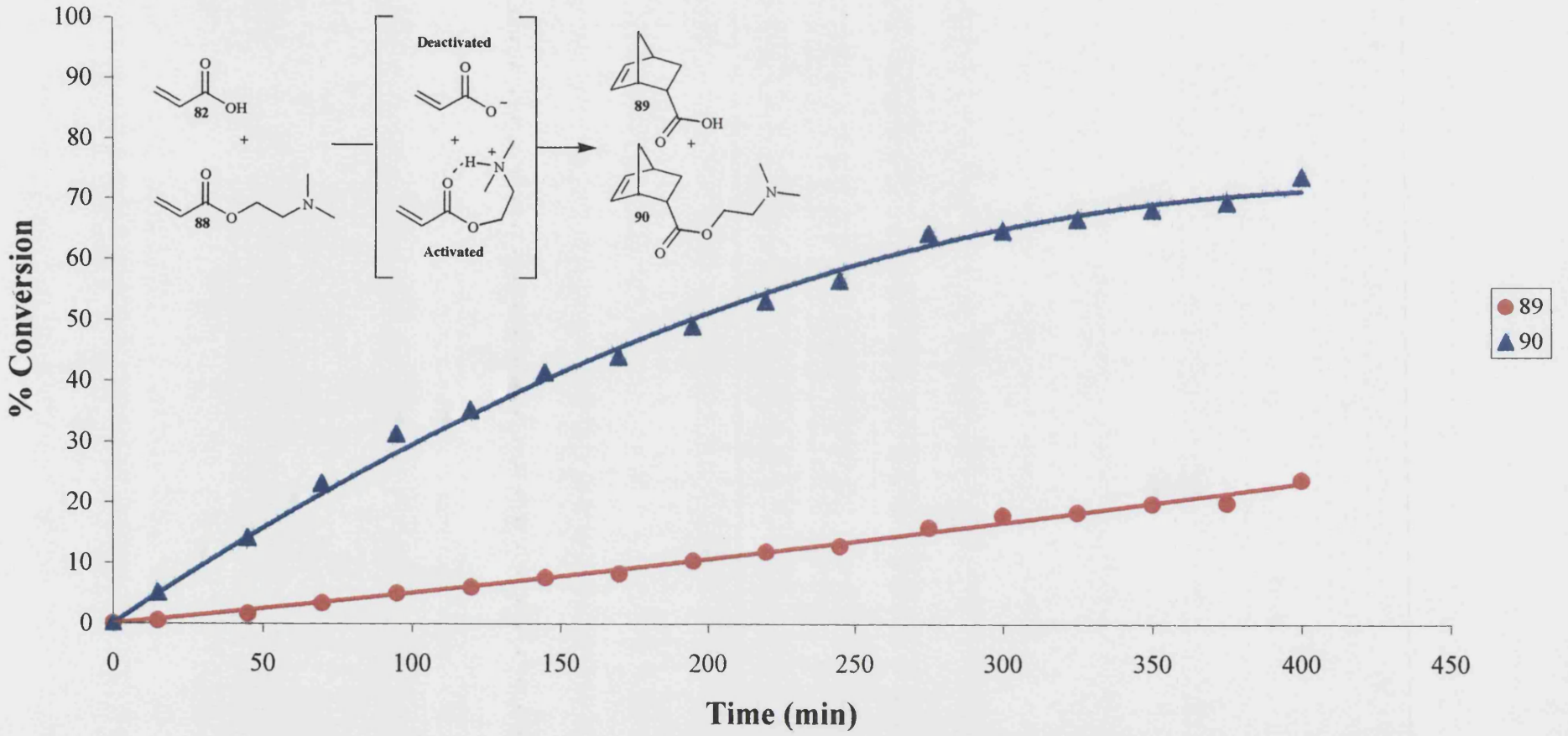
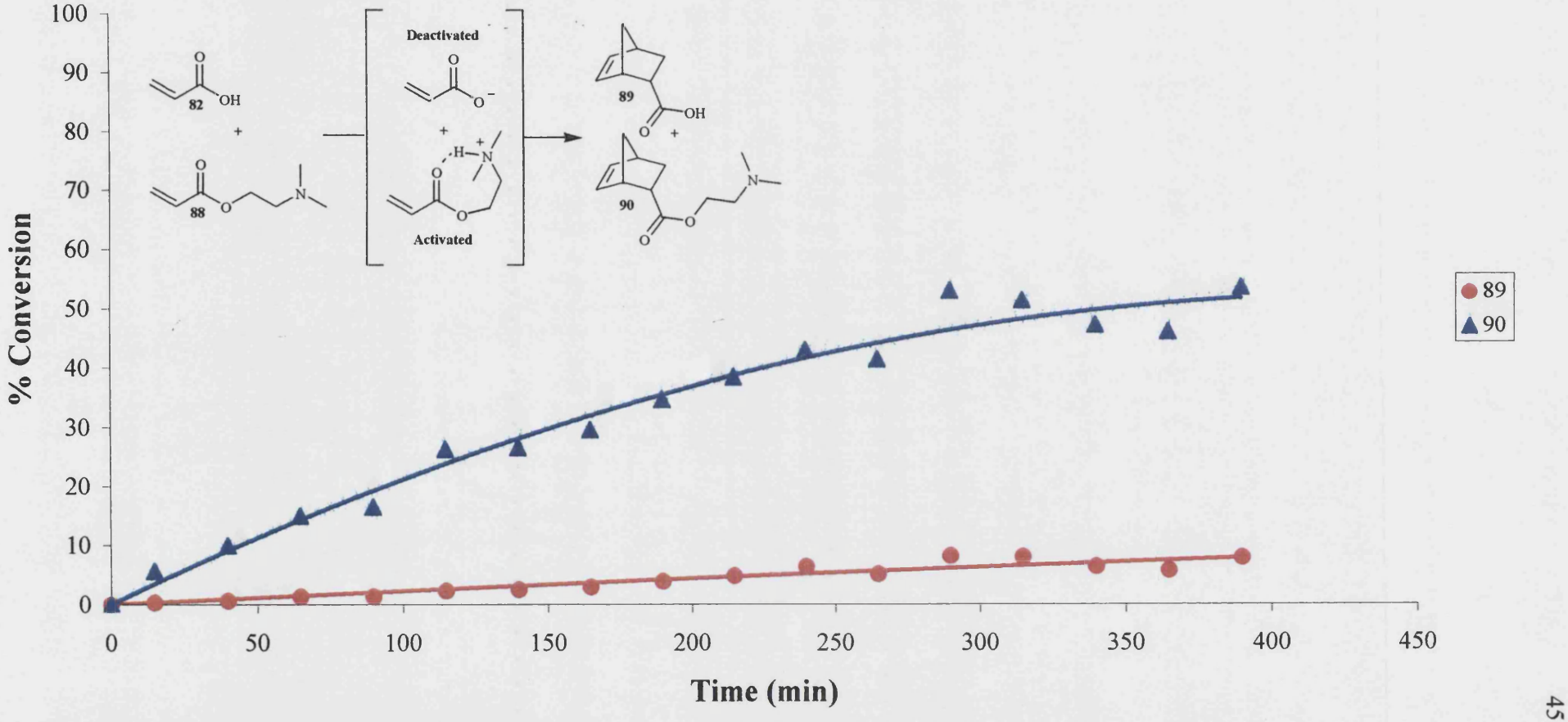


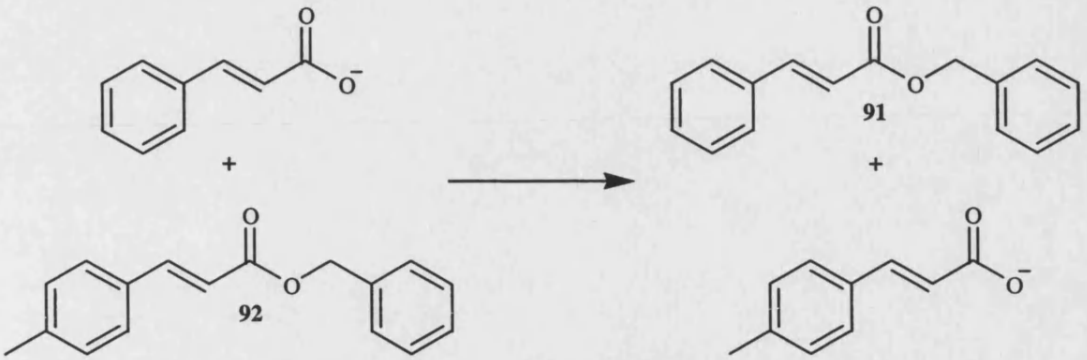
Figure 3: 1:2 Competition Reaction for formation of **89** vs **90**.



2.5 Reversible ester formation reaction

Esters are commonly made in a reversible manner from carboxylic acids *via* a simple acid catalysed reaction. This methodology is not applicable to the proposed cycle as, has been shown previously, to obtain a good rate difference between starting and auxiliary bound substrates, the starting substrate must be the carboxylate rather than the carboxylic acid. As such, any acid catalyst present would form the carboxylic acid from the carboxylate, reducing selectivity for the auxiliary catalysed pathway considerably. Therefore, it is necessary to obtain an equilibrium between carboxylates and esters.

It is widely known that esters can be made from carboxylates *via* a simple S_N2 reaction between the carboxylate and a suitable alkyl halide. The reversibility of this reaction was examined. Initial attempts looked at the reversible formation of methyl esters. When this proved fruitless benzyl esters were examined, as benzyl groups are known to undergo S_N2 reactions more readily than their simple alkyl counterparts.[74] In order to determine if any crossover had occurred the electronically identical benzyl (2*E*)-3-phenyl-2-propenoate **91** and benzyl (2*E*)-3-*p*-tolyl-2-propenoate **92** were examined. Analysis of the ^{1}H NMR spectra of a 1:1 mixture of ester **91** and ester **92** shows that the two compounds can be differentiated. The methyl group of ester **92** appears at 2.36ppm. By comparison of the integral of this peak and that for the benzyl groups of esters **91** and **92**, which appear at 5.24 and 5.25ppm respectively, any crossover that occurs can be determined. In addition, the alkene doublets for esters **91** and **92** do not coincide. If more than one species is present, two overlapping doublets at 6.41 to 6.52ppm and 7.67 to 7.76ppm are observed.



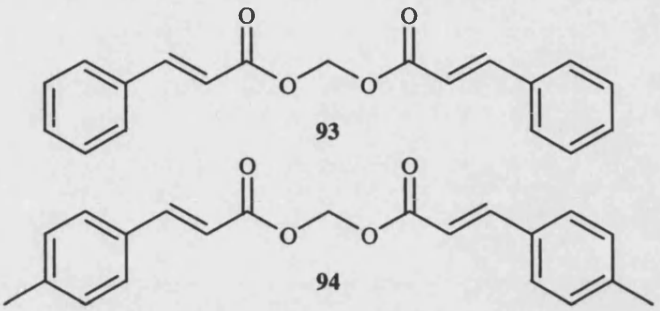
Scheme 40

Table 6: Attempted reversible ester formation reaction

Counterion	Solvent	Product
K^+	3:1 EtOH:H_2O	No Reaction
Cs^+	MeOH	Methyl Ester
NBu_4^+	DCM	**93**
NBu_4^+	Toluene	**94**

When the reaction was carried out with potassium salts, either in 3:1 EtOH:H_2O or in MeCN in the presence of 18-Crown-6, at room temperature or reflux, no reaction was observed by ^1H NMR analysis. Changing to caesium salts gave no crossover. However as these reactions were run in MeOH transesterification occurred to yield the corresponding methyl ester (Methyl: Benzyl = 5: 1) as confirmed by ^1H NMR analysis. The most interesting side reactions occurred when tetrabutylammonium salts were utilised. Overnight reaction of a tetrabutylammonium salt in toluene at reflux gave the butyl ester as confirmed by ^1H NMR analysis. Changing the solvent to DCM and carrying out the reaction at either room temperature or reflux produced the dimeric product methylidene dicinnamate **93** or methylidene di-(4-methyl)cinnamate **94** *via* nucleophilic attack of CH_2Cl_2. The ^1H NMR of these products are very similar to their benzyl ester counterparts except for the fact that the "benzyl" proton has moved from 5.24ppm for ester **92** to 6.02ppm in the dimeric species **94**, and no longer

corresponds to two protons. The identity of the dimers was fully disclosed as the mass spectrum corresponds well with that expected for the dimeric species. Similar products have been prepared before,[75] although more forcing conditions were used.



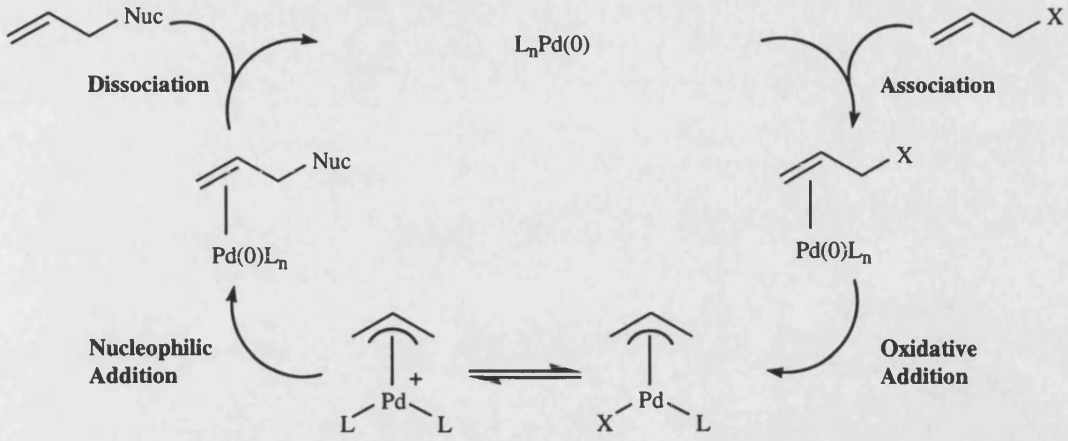
Scheme 41

Since a simple S_N2 reaction was not suitable as a method for reversible ester formation, the allylic substitution reaction was examined as an alternative.

2.6 Reversible ester formation *via* the allylic substitution reaction

The allylic substitution reaction is a powerful method for the formation of carbon-carbon and carbon-heteroatom bonds between allyl groups and nucleophiles. Palladium catalysed allylic substitution [76] is a versatile process encompassing a wide range of allyl systems and their nucleophilic partners due to the ease with which palladium is able to undergo oxidative addition and reductive elimination reactions. The basic process is illustrated in **Scheme 42**. The mechanism involves initial coordination of palladium(0) to the alkene, followed by an oxidative addition process to afford an intermediate η^3-allyl complex. In the presence of phosphine an equilibrium between a neutral and cationic complex results. The cationic complex is favoured by the use of bidentate phosphines ligands. Nucleophilic addition to the cationic complex is favoured and occurs at one of the allylic termini to afford the

palladium(0) complex of product. Dissociation of the palladium(0) liberates the product and regenerates the active palladium catalyst.



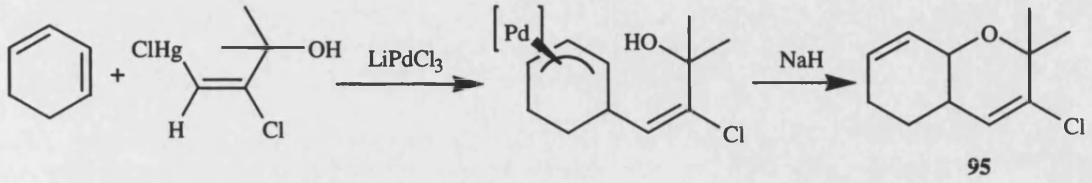
Scheme 42

A number of leaving groups such as sulfones, carbonates or halides, can be utilised in the reaction, although most examples use acetate leaving groups. The nature of the ligand employed has a significant effect on the course of the reaction. Generally, π-accepting ligands such as phosphines are used. By utilising ligands that contain two atoms with different π-accepting abilities, such as the P-N ligands,[77] regio- and stereocontrol can be obtained in the reaction.

A great number of nucleophiles can be employed, the most common being "soft" carbon nucleophiles such as the stabilised anions of various malonates. Under suitable conditions, heteroatom nucleophiles can also be used. For instance, oxygen nucleophiles have been employed in a number of different reactions.

Larock [78] has shown that (π-allyl)palladium, formed by the reaction of dienes with $LiPdCl_3$ and organomercurials bearing carboxylic acid or alcohol functionalities, readily undergo cyclisation on treatment with a suitable base. Deprotonation of the carboxylic acid or alcohol functionality generates a good nucleophile in close

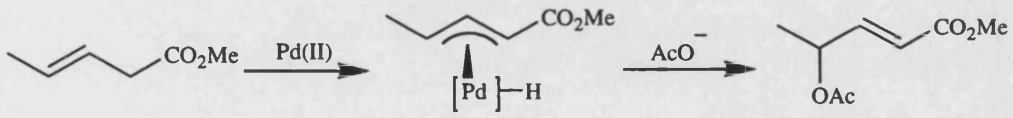
proximity to the allyl system. As expected, nucleophilic attack followed by dissociation of the palladium species generates the desired oxygen heterocycle **95**.



95

Scheme 43

In addition to alkoxides, acetates have also been used as nucleophiles. Tsuji [79] has shown that β,γ-unsaturated esters can be oxidised with $PdCl_2$, pentyl nitrile and KOAc to yield selectively γ-acetoxy-α,β-unsaturated esters **96**. Initial formation of a (π-allyl)palladium complex is followed by nucleophilic attack of the acetoxy anion. In this reaction, pentyl nitrile is used to recycle the Pd(0) produced back to the catalytically active Pd(II) species. Regioselectivity is obtained in this step, presumably influenced by the electron density of the π-allyl system.

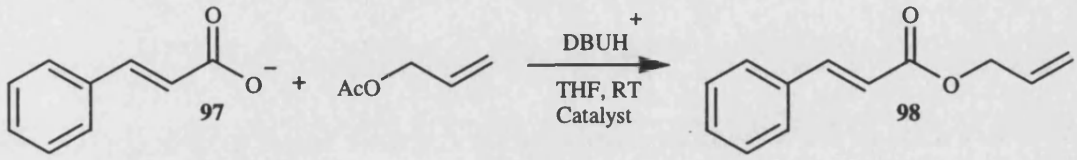


96

Scheme 44

Other groups have shown that acetoxy anions can act as nucleophiles.[80] In particular, allyl acetates can be isomerised in the presence of a suitable palladium catalyst by nucleophilic attack of acetate on the resultant π-allyl complex. Since many oxygen nucleophiles can be utilised in the allylic substitution reaction, it seems likely that allyl esters can be readily formed in this manner. Additionally, since acetoxy anions can be used as nucleophiles and as leaving groups, this reaction may be considered reversible. As such, the allylic substitution reaction could be used as a method for the reversible formation of allyl esters.

To prove whether the allylic substitution reaction can be utilised to form allyl esters, a standard reaction (**Scheme 45**) using cinnamate **97** as a nucleophile to form allyl (2*E*)-3-phenyl-2-propenoate **98** was investigated. Initially different catalysts were examined (**Table 7**). Using the air stable Pd_2dba_3 a poor yield of the desired product can be achieved as determined by ^1H NMR analysis. This can be increased by using $[(C_3H_5)PdCl]_2$ or $[CODIrCl]_2$. Although iridium catalysed allylic substitution [81] reactions are known in the literature this is one of the first examples that utilises a heteroatom nucleophile.[82]



Scheme 45

Table 7: Catalyst screening for formation of **98**.

Catalyst	Yield
Pd_2dba_3	16%
$[(C_3H_5)PdCl]_2$	26%
$[CODIrCl]_2$[a]	18%

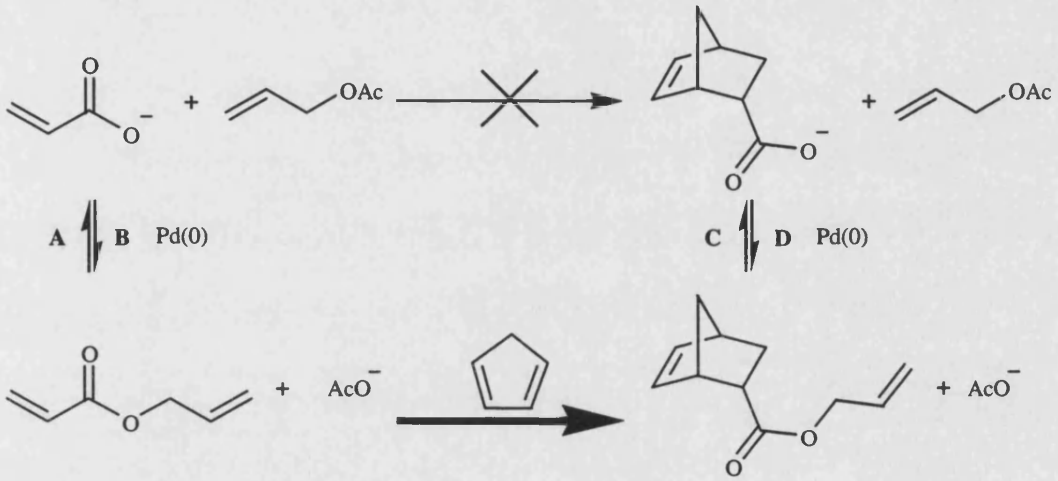
[a]: reaction run with $P(OPh)_3$ as ligand at reflux.

As $[(C_3H_5)PdCl]_2$ was shown to be the most active catalyst the effect of different counterions on the allylic substitution reaction was determined using this catalyst (**Table 8**). The use of metal counterions can be improved by incorporating crown ethers as chelating agents. Best results were obtained when organic soluble counterions are used (entries 6 and 7). The allylic substitution reaction appears to be a useful method for the formation of esters from carboxylates. Therefore, the possible application of this reaction to the proposed catalytic cycle was examined.

Table 8: Effect of counterion on the yield of **98**.

Counterion	Yield
Na^+	12%[a]
Na^+ & 15-Crown-5	18%[b]
K^+	9%[a]
K^+ & 18-Crown-6	14%[a]
BSA/KOAc	20%[a]
NBu_4^+	29%[b]
$DBUH^+$	26%[a]

[a]: reaction run in THF; [b]: reaction run in DCM.

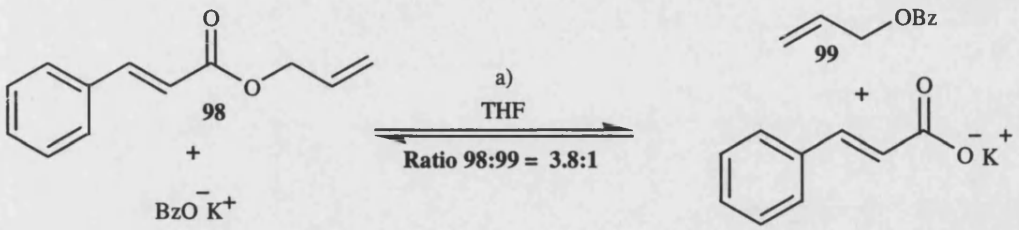


Proposed Cycle 1

The proposed catalytic cycle using carboxylates as the starting substrates, a catalytic amount of allyl acetate, and utilising the allylic substitution reaction as a key step, is shown above. As such the most abundant nucleophiles will be the starting carboxylate and the Diels-Alder carboxylate product. There will also be a mixture of allyl sources present; allyl acetate, allyl dienophile and allyl Diels-Alder adduct. As such, it would be advantageous to examine allylic substitution reactions that utilise all of these nucleophiles and allyl sources.

Initially, the transformations between starting and auxiliary bound substrates were examined. The results shown in **Table 7** and **Table 8** correspond to reaction **B** with

allyl acetate as the allyl source. To determine if this reaction is reversible, allyl ester **98** should be able to be cleaved using an acetate or benzoate nucleophile (Reaction **A**). As allyl benzoate **99** is less volatile than allyl acetate it will not be lost during workup of the reaction, therefore any allyl benzoate produced will be observed by ^{1}H NMR analysis and the relative ratios of allyl esters **98** and **99** can be determined.



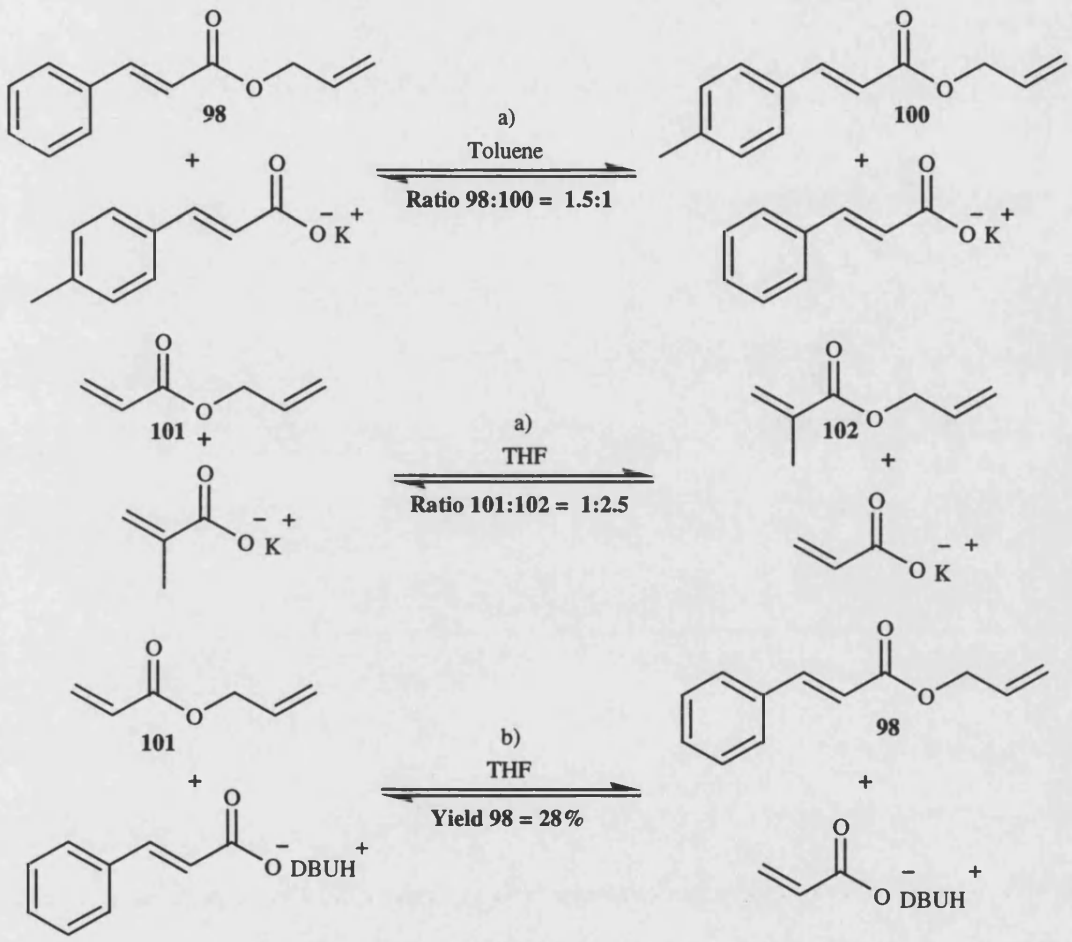
a) 5 mol% Pd_2dba_3, 20 mol% PPh_3, 1 Eq. 18-Crown-6, RT

Scheme 46a

When the cleavage of allyl ester **98** is carried out utilising a benzoate nucleophile the ratio of allyl esters **98** and **99** as determined by ^{1}H NMR analysis is 3.8:1, corresponding to 21% conversion. This shows that α,β-unsaturated allyl esters such as **98** can be successfully cleaved utilising a simple benzoate nucleophile. Both reactions **A** and **B** have been shown to proceed smoothly and as such an equilibrium between starting and auxiliary bound substrates should be possible.

As mentioned previously, allyl esters will be present in the reaction mixture as an alternative allyl source. A range of electronically similar α,β-unsaturated carboxylates and allyl esters were examined to see if they could be used in the allylic substitution reaction. This reaction will correspond to both reactions **A** and **B** in the proposed cycle as allyl esters will be prepared and cleaved in one step. When cinnamate nucleophiles and allyl esters are used, equilibrium can be established with ratios of allyl esters **98** and **100** close to equimolar. The ratio changes when acrylate and methacrylate substrates are used, however this may be attributed to the greater

volatility of the substrates leading to the ratio observed by ^{1}H NMR analysis being different to reality as some of the substrates may be lost on workup. These reactions can also be carried out utilising an iridium catalyst.

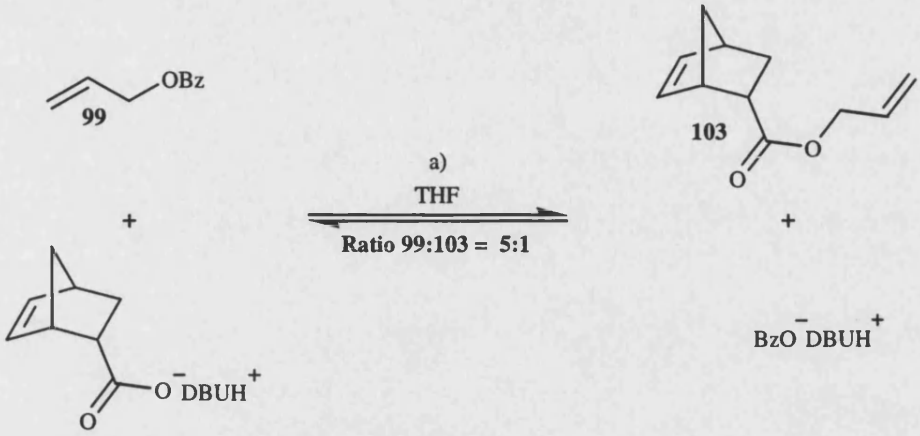


a) 5 mol% Pd_2dba_3, 20 mol% PPh_3, 1 Eq. 18-Crown-6, RT
b) 5 mol% $[CODIrCl]_2$, 20 mol% $P(OPh)_3$, Reflux

Scheme 46b

Therefore, as reactions **A** and **B** in the proposed cycle have been shown to proceed it is possible to establish an equilibrium between starting and auxiliary bound substrates. Next, reaction **D** was examined to see if allyl Diels-Alder adduct **103** could be prepared using an allylic substitution reaction. Using Pd_2dba_3 as a catalyst and allyl

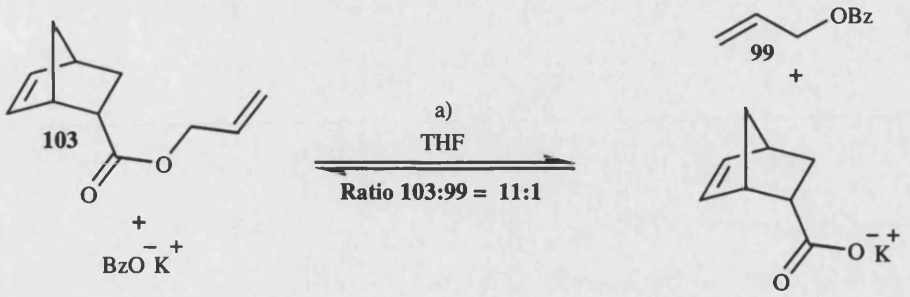
benzoate **99** as an allyl source, Diels-Alder adduct **103** can prepared in 17% conversion as determined by ^{1}H NMR analysis of the isolated allyl esters.



a) 5 mol% Pd_2dba_3, 20 mol% PPh_3, RT

Scheme 47a

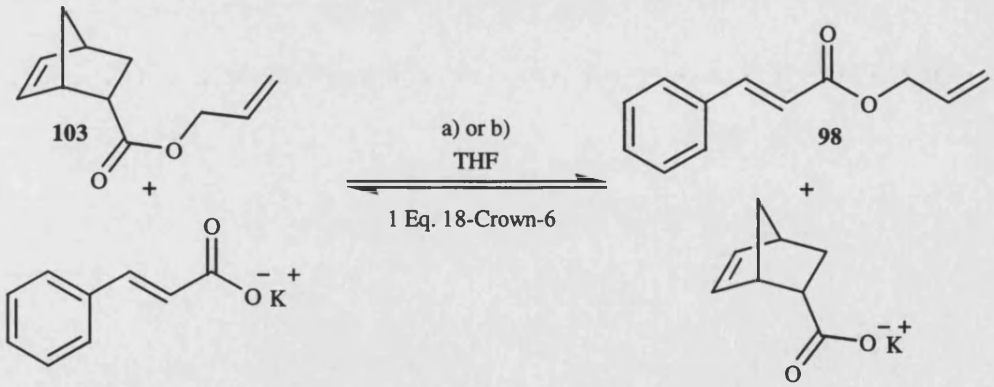
Reaction **C** in the proposed full cycle was also examined. Under analogous conditions for its preparation, Diels-Alder adduct **103** can be cleaved using a benzoate nucleophile as determined by analysis of the ^{1}H NMR of the isolated mixture of adduct **103** and allyl benzoate **99**. This analysis shows the reaction to proceed with approximately 8% conversion. The only limitation may be the apparent difficulty in cleavage of the allyl Diels-Alder adduct **103**. In the proposed cycle, rapid cycloaddition of the resultant allyl ester **101** should shift the equilibrium containing this product towards complete reaction of starting material *via* consumption of the product. This in turn generates an excess of allyl Diels-Alder adduct **103**, forcing the right-hand equilibrium towards cleavage. As such, the overall reaction should proceed smoothly to give a good yield of the desired product.



a) 5 mol% Pd_2dba_3, 20 mol% PPh_3, 1 Eq. 18-Crown-6, RT

Scheme 47b

Both reactions **C** and **D** have been shown to proceed smoothly, and as such it should be possible to establish an equilibrium between the auxiliary bound Diels-Alder adduct and the desired final product of the proposed cycle. Since the reaction mixture will also contain a substantial amount of the α,β-unsaturated carboxylate nucleophile, the ability of this substrate to cleave allyl Diels-Alder adduct **103** was examined. Indeed, this reaction proceeds smoothly in the presence of Pd_2dba_3 as a catalyst to give a mixture of allyl Diels-Alder adduct **103** and allyl cinnamate **98**, as determined by ^1H NMR analysis. The conversion can be improved from 9% to 13% by utilising an iridium catalyst.

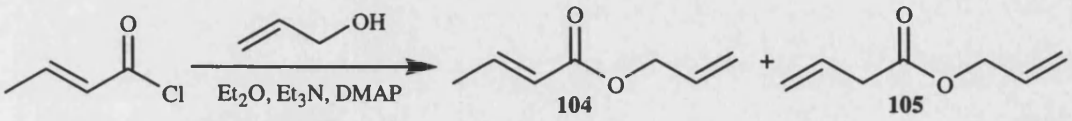


a) 5 mol% Pd_2dba_3, 20 mol% PPh_3, RT, **Ratio 103:98= 10:1**
b) 5 mol% $[CODIrCl]_2$, 20 mol% $P(OPh)_3$, Reflux, **Ratio 103:98= 7:1**

Scheme 47c

Reactions were also attempted with crotonate derivative **104**. Attempts to produce authentic samples of this compound were complicated as under the basic conditions

required isomerisation occurs to yield a mixture of the unconjugated adduct **105** and the conjugated **104** as determined by ^{1}H NMR analysis. This isomerisation has previously been utilised to generate mixed vinylketene acetals as dienes for the Diels-Alder reaction.[83]



Scheme 48

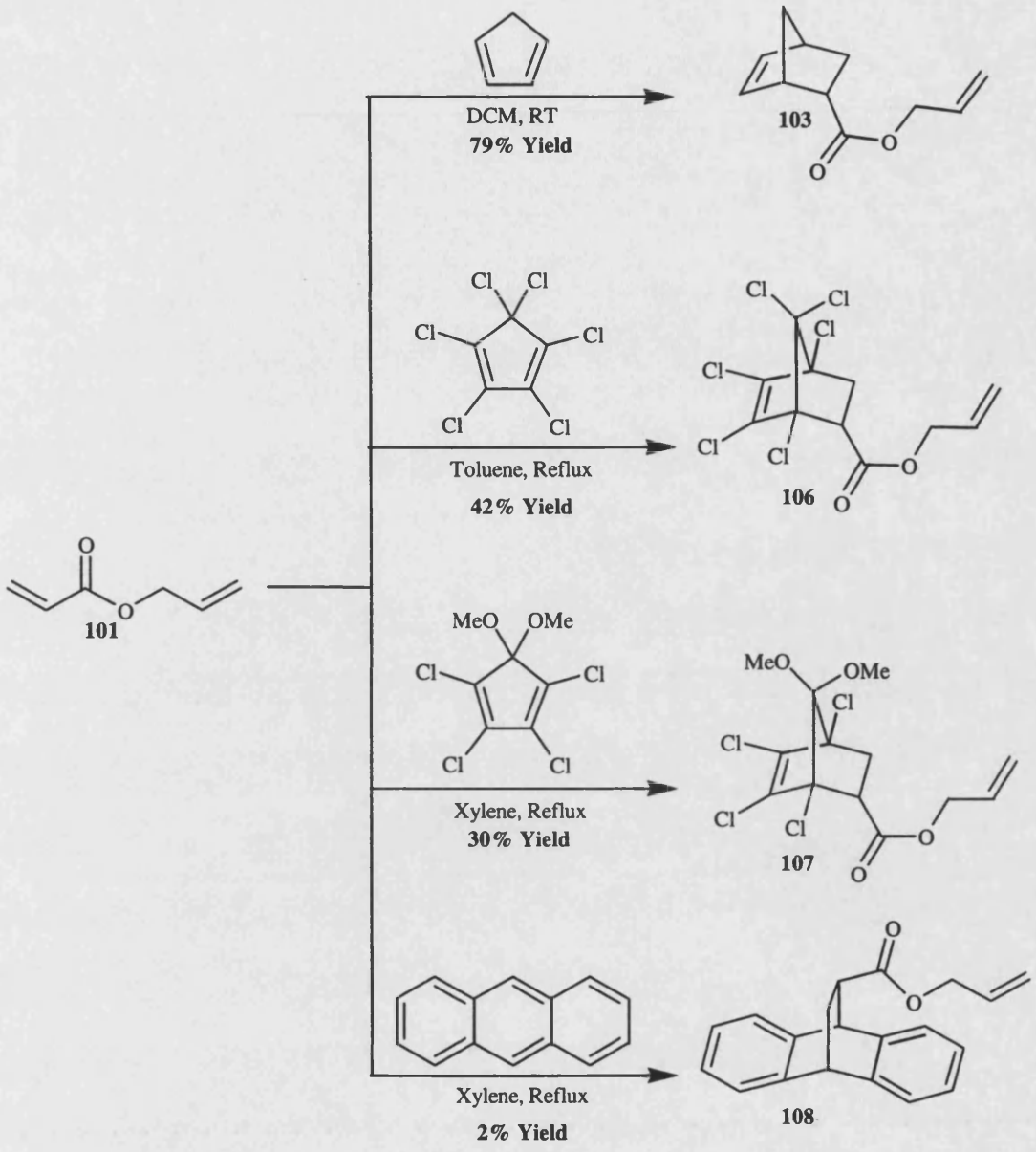
2.7 Diels-Alder reaction of allyl acrylate 101

The ease of Diels-Alder reaction of allyl acrylate **101** was examined with a variety of dienes. In comparison to other esters previously examined, allyl acrylate **101** undergoes cycloaddition with cyclopentadiene at room temperature to produce the desired Diels-Alder adduct **103** in 79% yield (**Scheme 49**). Interestingly, the *endo* and *exo* isomers of Diels-Alder adduct **103** were readily separable by flash column chromatography. This is not possible for all Diels-Alder adducts and the ease of separation for this product may be due to some π-interaction between the allyl group and the norbornene double bond. The isomers were assigned as *endo* and *exo* by analysis of the respective ^{1}H NMR spectra. The *endo* isomer was so assigned as the peaks corresponding to the norbornene alkene protons are different, presumably due to steric effects caused by the ester functionality, occurring at 5.93ppm and 6.17ppm respectively. The norbornene alkene protons for the *exo* isomer are equivalent and therefore only one peak is observed in the ^{1}H NMR at 6.04ppm.

In addition other less reactive dienes were examined. Adding electron withdrawing groups to cyclopentadiene makes it less reactive. Both hexachlorocyclopentadiene and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene give the desired Diels-Alder

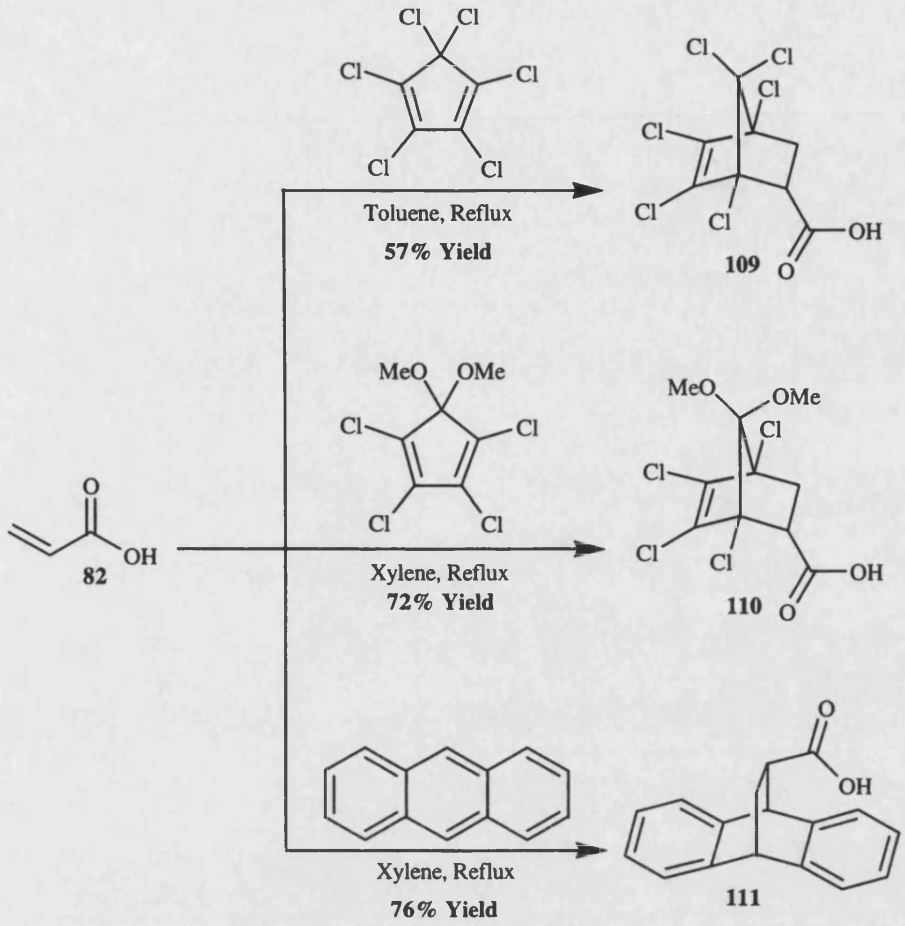
adducts **106** and **107** in only moderate yield even under quite harsh conditions. Anthracene is a diene that has found certain applications in cycloaddition chemistry, the driving force for which is the higher aromatic nature of two isolated benzene rings over that of the conjugated anthracene system. The adducts also undergo pyrolytic retro-Diels-Alder reactions at temperatures in excess of 250 °C.[84] In the reaction of allyl acrylate **101** with anthracene, elevated temperatures are again required to give a very poor yield of the desired cycloadduct **108**. This yield can be improved to 10% by running the reaction in toluene at reflux in a sealed pressure tube.

The cycloaddition of the less reactive allyl cinnamate **98** with cyclopentadiene was also examined. When the reaction was carried out in DCM at reflux, no Diels-Alder adduct was isolated. This suggests that quite forcing conditions are required to carry out this reaction and therefore it was decided to look solely at the reactions of acrylates at this time.



Scheme 49

Authentic samples of the acid analogues of these products were made in a similar manner. In all cases yields were increased from that for the formation of the corresponding allyl esters. This further supports the argument that carboxylic acid substrates are more reactive than their ester counterparts. As before, by carrying out the anthracene reaction in toluene at reflux in a sealed pressure tube the yield of adduct **111** can be increased, this time to 87%.

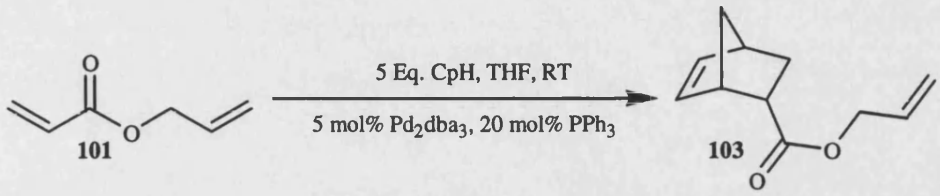


Scheme 50

When the reaction of the potassium salt of acrylic acid and cyclopentadiene is carried out in the presence of 18-Crown-6, no Diels-Alder adduct is observed after 24 hours as determined by ^{1}H NMR analysis. Comparing this result to the 79% yield observed for the reaction of allyl acrylate suggests that a good rate difference exists between these substrates and as such they would be suitable for the proposed cycle.

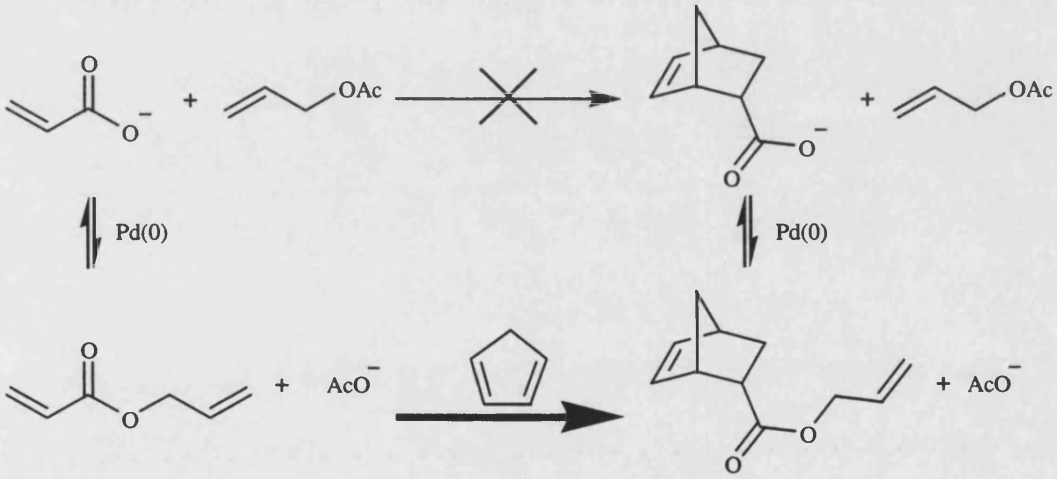
When the reaction between acrylic acid **82** and anthracene is carried out in the presence of either DBU or NaH less than 5% product is observed by analysis of the ^{1}H NMR spectra. Formation of the carboxylate again reduces the reactivity of the acid substrate. However in this case the background Diels-Alder reaction occurs in a comparable amount to that for the reaction of allyl acrylate. As such, the use of anthracene in the proposed cycle may be limited.

The Diels-Alder reaction of allyl acrylate **101** and cyclopentadiene was carried out in the presence of Pd_2dba_3/PPh_3. Apart from a darkening of the reaction mixture the reaction proceeds as normal to give the desired cycloadduct **103**. This suggests that the presence of palladium does not affect the Diels-Alder reaction.



Scheme 51

2.8 Attempted full catalytic cycle



Proposed Cycle 1

Each step of the proposed full cycle has been proven individually. Therefore attempts were made to generate a full cycle whereby the allylic substitution reaction is the key step. Many attempts were made following the same general experimental method. Palladium catalyst and phosphine are mixed in DCM under nitrogen for 30 minutes. This is added to a solution of acrylic acid and DBU in DCM. Allyl acetate is added and the reaction is left at room temperature under nitrogen for 3 hours when freshly cracked cyclopentadiene is added. The reaction is left overnight and then worked up.

Any carboxylic acid products isolated by column chromatography are analysed by ^1H NMR.

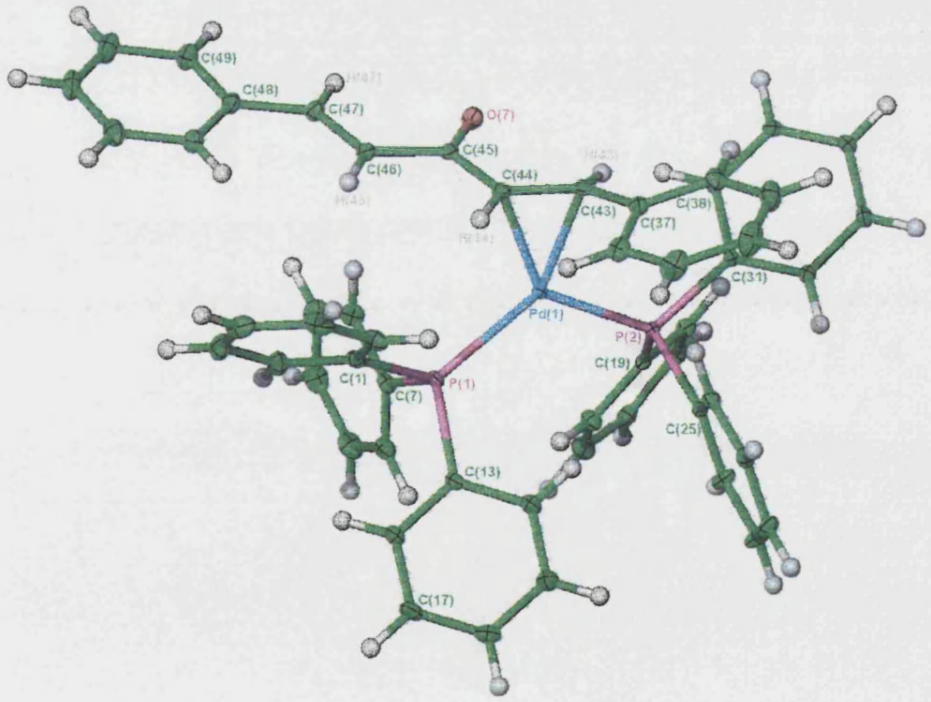
Initial reactions were run using Pd_2dba_3 and PPh_3 with 20 mol% allyl acetate. Unlike the isolated Diels-Alder reactions, the reaction turned black after a few hours. Following work-up very small amounts of acidic products were isolated. By NMR analysis, no Diels-Alder acid **83** could be observed. The isolated material was an orange oil and its ^1H NMR and GC traces were very chaotic containing many more peaks than expected leading to very little useful data being obtained.
This reaction was re-run using 20 Eq. allyl acetate, again yielding no product. Allyl benzoate was also utilised to no effect. Changing the ligand to the bidentate DPPE also gave no improvement, nor did changing the counterion to K^+ or Na^+.
Analysis of the organic layer containing any allyl esters present suggested that allyl acrylate **101** and the corresponding Diels-Alder adduct **103** were being formed. Indeed when the reaction is run starting from the allyl Diels-Alder adduct **103** in the presence of cyclopentadiene and Pd_2dba_3/PPh_3, the resultant Diels-Alder acid **83** can be isolated in 60% yield. This suggests that the allylic substitution reaction is failing at prolonged reaction times. Allylic substitution does occur to form allyl acrylate **101** however this equilibrium lies in favour of the starting material. Diels-Alder reaction forms Diels-Alder adduct **103** but only in small amounts. If the equilibrium for the cleavage of Diels-Alder adduct **103** *via* the allylic substitution reaction lies in favour of the allyl ester, formation of the overall product will be slow. As it appears that the allylic substitution reaction slows with time, formation of the overall product may be difficult to detect.

One possible method for deactivation of the allylic substitution is formation of a complex between diene and palladium. In all full cycles attempted addition of cyclopentadiene was accompanied by a gradual darkening of the reaction mixture and formation of a black precipitate. When hexachlorocyclopentadiene was utilised the colour change was fast and dramatic, suggesting electron withdrawing groups stabilise any complex formed. The formation of such a complex would not, as observed, affect the Diels-Alder reaction as a large excess of diene is added meaning any removed by palladium will be insignificant. However, addition of any diene to the allylic substitution reaction will result in loss of activity.

To check this hypothesis, the Diels-Alder reaction of allyl acrylate and cyclopentadiene, anthracene and hexachlorocyclopentadiene were carried out as before, but this time 5 mol% $[(C_3H_5)PdCl]_2$ and 10 mol% PPh_3 were added to the reaction. After 24 hours, 1 Eq. cinnamate nucleophile was added and the reaction was left for a further 24 hours. If the palladium catalyst is still active, allyl cinnamate **98** should be produced. ^1H NMR analysis suggested that in all three cases, none was formed, confirming that the presence of a variety of dienes deactivates the active palladium species.

Attempts were made to isolate the palladium complex responsible for this deactivation by adding cyclopentadiene to a stirred solution of Pd_2dba_3 and 2 Eq. PPh_3 in DCM. After six hours, the solvent was removed *in vacuo* to give a mixture of a red/orange precipitate and a black precipitate. The red/orange precipitate was soluble in ether, whereas the black precipitate was not, and as such the black precipitate was removed by filtration. Attempts to purify the black precipitate *via* recrystallisation were unsuccessful and analysis of the NMR of the crude product could not disclose its

structure. Layering hexane onto a solution of the red/orange precipitate in ether allowed a crystal of this palladium complex to be obtained. The identity of this product was determined to be structure **1** by X-ray crystallography as the red crystal decomposed when it was dissolved in any deuterated solvent meaning no NMR analysis could be carried out. This complex should be able to participate in the allylic substitution reaction, although as it is formed in low yield (9%), a majority of the palladium has been decomposed by the presence of the diene, presumably to form the black precipitate also observed. This suggests that the allylic substitution reaction is slowed considerably since most of the active palladium species has been removed from the reaction. Similar complexes have already been isolated,[84a] however the crystal structure of the palladium complex has not been solved thus far.



$Pd(dba)(PPh_3)_2$

Structure 1

As a way of proving whether the scientific concept behind the proposed full cycle is valid the allyl esters produced were hydrolysed under basic conditions to give the corresponding carboxylic acids. Initial reactions showed that with or without palladium present Diels-Alder adduct **103** can be hydrolysed to carboxylic acid **83** in quantitative yield. When adapted to the full cycle methodology, reaction utilising catalytic amounts of allyl acetate showed no Diels-Alder adduct **83** after hydrolysis. However, when 20 Eq. of allyl acetate is used the desired Diels-Alder adduct **83** can be isolated in good yield. Care should be taken when quoting these yields as even though the products were purified by column chromatography, ^{1}H NMR and GC analysis showed that the products still contained impurities. Indeed the isolated products, although one spot by TLC, were orange or brown in colour compared with the colourless oil when Diels-Alder adduct **83** is obtained via other methods.

Table 9: Effect of various catalysts on the yield of **83** after hydrolysis

Catalyst	Yield of 83
$[(C_3H_5)PdCl]_2$	38%
$Pd(OAc)_2$	30%
$PdCl_2$	53%
$(PhCN)_2PdCl_2$	90%
$CODPdCl_2$	90%

It appears as if the overall scientific concept of this proposed cycle is valid, however the actual engineering required to complete it remains elusive. As an alternative, activating groups other than esters were examined.

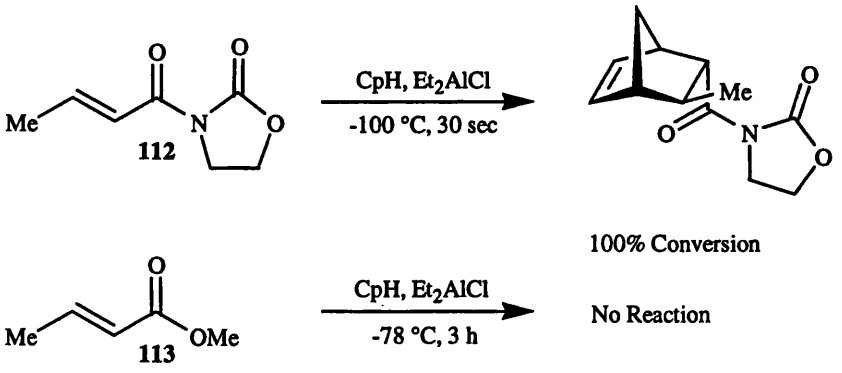
Chapter 3

Oxazolidinones As Activating Groups

3) Oxazolidinones As Activating Groups

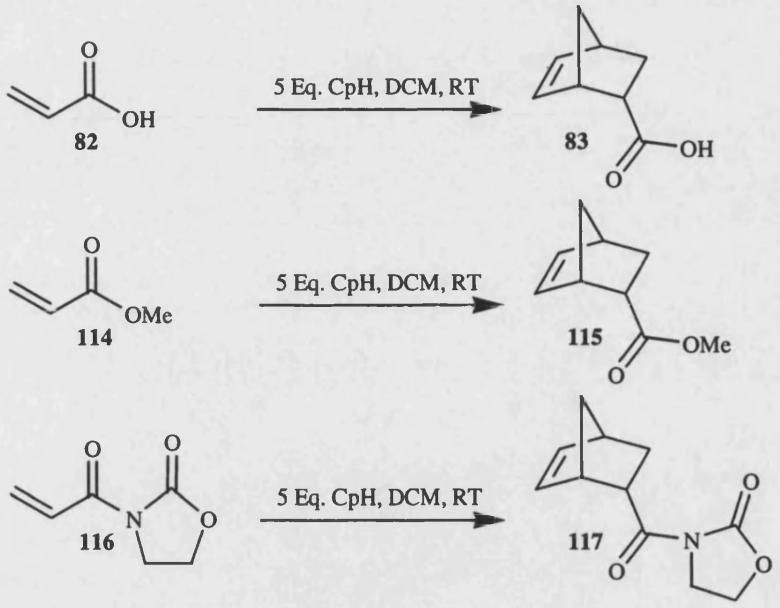
3.1 Nature of the Diels-Alder reactions of oxazolidinone substrates

As was shown in the introduction oxazolidinones are among the most widely used chiral auxiliaries in organic synthesis today. There are many enantiomerically pure oxazolidinones that can control the stereochemistry of cycloadditions to give products with excellent diastereoselectivity. In addition, they are much more reactive than their ester counterparts due to their more strongly electron withdrawing nature. Utilising a suitable Lewis acid can enhance this effect considerably. For instance, treatment of unsubstituted crotonyl oxazolidinone **112** with excess cyclopentadiene and 1.4 Eq. of diethylaluminium chloride in DCM at –100 °C leads to the formation of a single cycloadduct in quantitative yield within a few seconds.[46d] By comparison, methyl crotonate **113** when treated under similar conditions (-78 °C, 3 h) showed no reaction.



Scheme 52

As the lone pair on nitrogen is delocalised into the oxazolidinone carbonyl group, it is less available for conjugation with the amide carbonyl group. As such the imide functionality is a better electron-withdrawing group than an ester and therefore undergoes Diels-Alder reactions readily. Although Lewis acids help this effect, the rate of the Diels-Alder reaction of simple acrylates was investigated in their absence.



Scheme 53

The rate of formation of **115** was calculated by GC using dodecane as an internal standard. This method was unsuccessful for determination of the rate of formation of **117**, possibly as the reaction is very fast leading to any errors being more important. As an alternative, HPLC analysis was attempted. Prior calibration with known samples enabled the relative ratio of starting material and product to be determined. This enabled easy calculation of the desired rate constant. The calculated data, shown in **Appendix 3**, allows rate curves (**Figure 4**) for each reaction to be plotted.

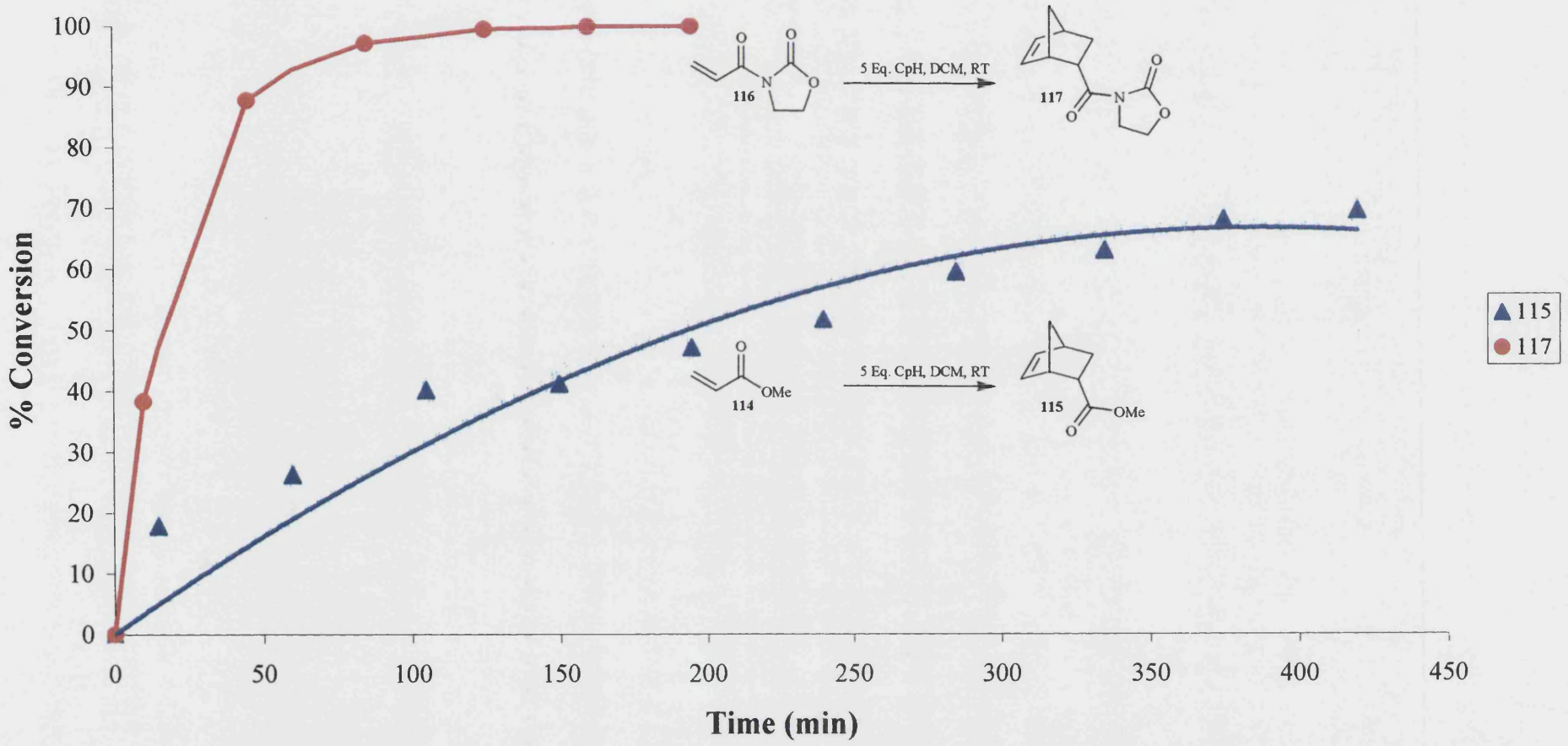
Table 10: Relative rate of formation of **115** and **117**

Product	Relative Rate
83	1000
115	208
117	2879

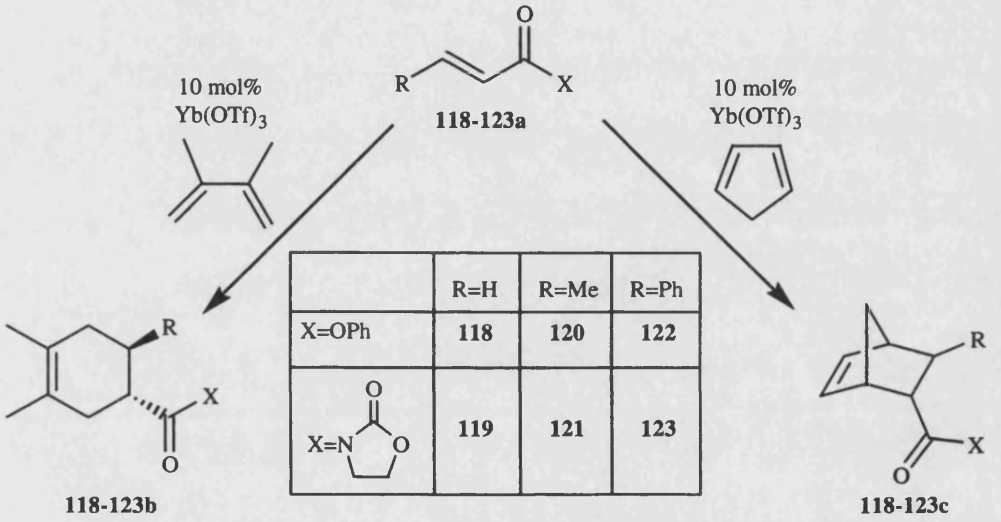
The rate of formation of ester **115** is comparable to that for other esters investigated. Due to its strongly electron withdrawing nature, changing the activating group to an oxazolidinone increases the rate of reaction considerably. Indeed, formation of the oxazolidinone **117** is faster than that for the corresponding carboxylic acid substrate

83. In addition, both Diels-Alder adducts **115** and **117** can be isolated in good yield once the reaction is complete.

Figure 4: Rate of reaction for formation of **115** and **117**



Moving to the less reactive cinnamate substrate **122a** retards the reaction considerably and under identical conditions, no reaction is observed. Most examples of Diels-Alder reactions of oxazolidinone substrates are carried out at low temperature in the presence of a suitable Lewis acid. Ytterbium triflate has found considerable use as a Lewis acid in many Diels-Alder reactions,[85] and as such its use in the cycloaddition of various oxazolidinone substrates was examined. For comparison, the analogous phenyl esters were also investigated.



Scheme 54

Table 11: Comparative yields of $Yb(OTf)_3$ catalysed Diels-Alder reactions of **118-123**

Substrate	Yield of b	Yield of c
118	0%	100%
119	100%	100%
120	0%	16%
121	0%	100%
122	0%	0%
123	0%	97%

To obtain a workable catalytic cycle, a good rate difference must be obtained between ester and oxazolidinone substrates. The reactions of cyclopentadiene with all substrates gave interesting results. Phenyl acrylate **118a** gives complete conversion into cycloadduct **118c** suggesting it is too reactive for use in the proposed full cycle.

In contrast, phenyl crotonate **120a** and phenyl cinnamate **122a** show poor reactivity. By comparison the analogous oxazolidinone substrates **121a** and **123a** undergo virtually quantitative conversion into the corresponding products.

Phenyl acrylate **118a** is unreactive when the diene is changed to 2,3-dimethylbutadiene, however the more reactive oxazolidinone substrate **119a** undergoes complete conversion. Substrates **120a** to **123a** are completely unreactive under these conditions. These results are a good demonstration of the effects of substituents on the rates of Diels-Alder reactions. Oxazolidinone substrates are more reactive than the corresponding esters due to the greater electron withdrawing nature of the imide functionality. By adding an alkyl group to the β-position of the dienophile the reactivity can be considerably reduced. Combining these effects enables good selectivity for the auxiliary bound substrate to be obtained.

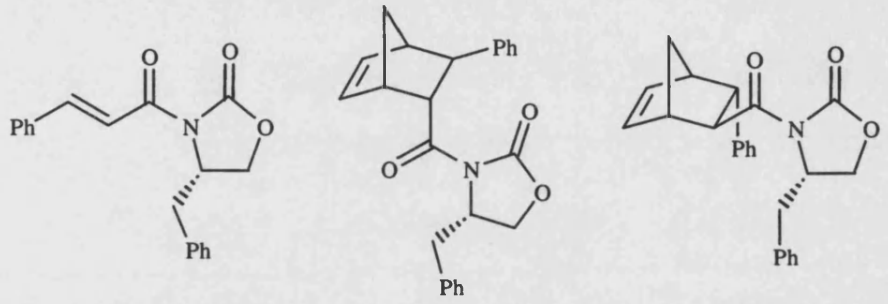
The large rate differences that can be obtained should enable crotonate and cinnamate substrates with cyclopentadiene and acrylates with 2,3-dimethylbutadiene to be used in the proposed full cycle.

As in the production of allyl crotonate **104**, formation of both phenyl crotonate **120a** and oxazolidinyl crotonate **121a** under basic conditions is accompanied by isomerisation to the unconjugated product. This only occurs to a small amount for oxazolidinone **121a**, but is important for ester **120a**, however this can be overcome by forming the phenyl ester using Dean-Stark methodology.

Analytically pure samples of Diels-Alder adduct **122c** can be obtained by carrying out the reaction without a catalyst in toluene at reflux to yield 10% product. Alternatively, reaction with 10 mol% $Yb(OTf)_3$ in DCE at reflux gives <5% conversion after 18 h. This suggests that **122a** would make a good starting point for investigation, as it is highly unreactive to the Diels-Alder reaction. Under similar conditions (DCM, reflux,

10 mol% $Yb(OTf)_3$, 6 h) **123c** is formed in >90% yield in a much shorter reaction time.

Asymmetric *N*-acyl oxazolidinone **124** can also be utilised to give products with enhanced stereoselectivity. It is possible to produce four stereoisomers in the Diels-Alder reaction of the cinnamate substrate **124** with cyclopentadiene as both the carbonyl and phenyl functionalities can adopt *endo* and *exo* positions. Column chromatography allows separation of two fractions, both shown by spectroscopic analysis to be a mixture of two diastereomers. ^{1}H NMR analysis of the products allowed the proposed structures **125** and **126** to be determined.



124 **125** **126**

Scheme 55

In acrylate Diels-Alder adducts, the peaks corresponding to the alkene protons in the *exo* products are coincident as the carbonyl group is far enough away so that the protons are in identical environments. In the *endo* adducts, interactions between the carbonyl group and the alkene cause the protons to be non-identical and as such the peaks corresponding to these protons appear separately in the ^{1}H NMR spectra. ^{1}H NMR analysis of cycloadducts **125** and **126** suggested that both contained a product which was a mixture of *endo* and *exo* carbonyl groups as the peaks in the region 5.95 to 6.60ppm corresponding to the alkene protons show that two environments exist. The phenyl group can also adopt either *endo* or *exo* positions. Since adducts **125** and **126** are mixtures of *endo* and *exo* carbonyl groups, the only difference between them

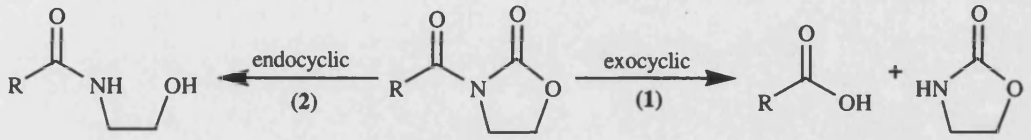
can be the relative orientation of the phenyl group. Analysis of the ^{1}H NMR spectra of cycloadduct **126** suggests the phenyl group adopts an *endo* position as the peak corresponding to the CH of the oxazolidinone ring is split in a ratio corresponding to the *endo*:*exo* ratio of the carbonyl group. Presumably, when the carbonyl group is in the *exo* position the proximity of the oxazolidinone ring to the phenyl group causes the peak for this proton to shift by approximately 0.1ppm. When the carbonyl group is in the *endo* position, the peak occurs in the expected position showing that it is unaffected by the proximity of the phenyl group. Similar analysis of cycloadduct **125** shows that the oxazolidinone CH peak is unaffected, suggesting that the phenyl group is in the *exo* position and is too far away from the oxazolidinone ring to affect the CH proton.

Interestingly, when the reaction is carried out in DCE at reflux rather than DCM, the selectivity favours cycloadduct **126**. At the elevated temperature, enough energy is available to overcome any steric barriers and favour production of the adduct where secondary orbital overlap between the alkene and cinnamate phenyl group is a stabilising factor.

Investigation of the relative rates of Diels-Alder reactions suggest that good rate differences can be obtained between phenyl and oxazolidinyl acrylate with 2,3-dimethylbutadiene and phenyl and oxazolidinyl crotonate and cinnamate with cyclopentadiene, and therefore these substrates warrant further examination. For the proposed cycle to work, methodology must be developed whereby ester functionalities can be transformed into the corresponding oxazolidinone substrates and *vice versa*.

3.2 Transesterification of oxazolidinones and esters

The transformation between auxiliary bound and starting substrates could be achieved using known methods for transesterification.[86] Indeed in analogy with ester chemistry, oxazolidinones can be changed into their benzyl ester counterparts with either LiOBn or $Ti(OBn)_4$.[48, 49] The nucleophilic cleavage of unhindered *N*-acyl oxazolidinones undergoes exocyclic cleavage to give the desired product (**Equation 1**). However, when R is larger or α-branched, the undesired endocyclic cleavage of the oxazolidinone ring is predominant with basic reagents (**Equation 2**). Utilising peroxide reagents can avoid endocyclic cleavage,[51] but the use of this reagent on a large scale may be hazardous due to its explosive nature.

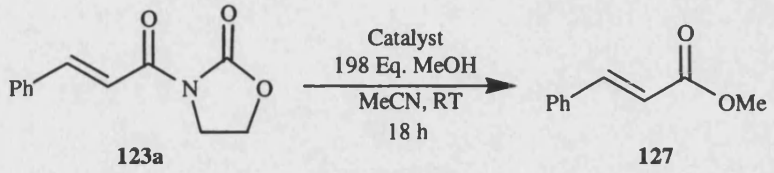


Scheme 56

Mild methods that utilise alcohols in the presence of Lewis acid catalysts have been developed. Various oxazolidinone substrates have been cleaved to their corresponding esters in good yield and with no epimerisation of the newly formed chiral centres by using mixtures of $MeOH/Sm(OTf)_3$,[87] $BnOH/LaI_3$,[88] and more recently mixtures of MeOH and either $[^tBu_2SnCl(OH)]_2$, $MgBr_2$ or $Sc(OTf)_3$.[89] These methods proceed without using basic metal alkoxide, making this method characteristic.

If this methodology can be utilised to transform between starting and auxiliary bound substrates, the desired equilibria could be obtained. In addition, if a suitable Lewis acid is utilised, it could also catalyse the Diels-Alder reaction, making this a very efficient method for obtaining a cycle where chiral auxiliaries can be used in a catalytic manner. As such several catalysts were screened to see if they could also

carry out the methanolysis of oxazolidinyl cinnamate **123a**. Yields were calculated by HPLC analysis following prior calibration with known standards.



123a **127**

Scheme 57

Table 12: Methanolysis of oxazolidinyl cinnamate **123a**

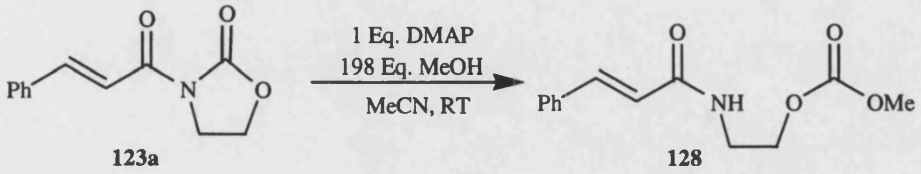
Catalyst	Yield with 1 Eq.	Yield with 10 mol %
None	No Reaction	No Reaction
Acetic Acid	No Reaction	No Reaction
PPTS	No Reaction	No Reaction
DMAP	62%*	8%*
$Ti(O^iPr)_4$	5%	10%
LaI_3	100% [a]	100%
$EuCl_3$	60%	25%
$ZnCl_2$	50%	No Reaction
$Cu(OTf)_2$	No Reaction	No Reaction
$ZrCl_4$	47%	51%
$Eu(OTf)_3$	100%	99%
$Sc(OTf)_3$	100%	80%
$Yb(OTf)_3$	100% [b]	95% [a]
$La(OTf)_3$	25% [b]	Not Run

[a]: Reaction complete in less than 3 h; [b]: In 7 h; * Side product also observed.

The use of simple protic acids such as acetic acid and pyridinium *p*-toluenesulphonate (PPTS) gave no methanolysis, nor did the widely used Diels-Alder catalyst $Cu(OTf)_2$. $Ti(O^iPr)_4$ has been utilised as a transesterification catalyst but under these reactions showed little activity. Work [89] published after this study was complete also showed that $Ti(O^iPr)_4$ was an unsatisfactory catalyst for the transformation (38% yield after 30 h at 85 °C). Both $ZnCl_2$ and $ZrCl_4$ were successful in carrying out this transformation, particularly when used in stoichiometric amounts.

DMAP has been examined as a catalyst for the methanolysis of the Diels-Alder adduct **121c**.[90] It was found to be ineffective, however by utilising the more polarisable carboxthioimide derived adduct the corresponding methyl ester could be obtained in

excellent yield. As steric effects may be responsible for the lack of cleavage of Diels-Alder adduct **121c**, DMAP was examined in the cleavage of cinnamate **123a**. It was found that when 1 Eq. of DMAP is utilised, methanolysis does occur. However, a by-product can also be isolated. ^{1}H NMR analysis suggests that the product is the ring-opened adduct **128**. This structural assignment is confirmed by IR and mass spectroscopy analysis of the purified product, which can be isolated in 39% yield.



123a **128**

Scheme 58

As was previously mentioned, LaI_3 was found to be an efficient catalyst and when utilised under this particular set of reaction conditions was found to be excellent. As such, other commercially available lanthanide Lewis acids were examined. $EuCl_3$ was found to be a moderate catalyst however activity could be increased considerably increased by changing to the triflate analogues. Both $Eu(OTf)_3$ and $Yb(OTf)_3$ were found to be truly excellent catalysts, even when utilised at 10 mol% levels. In addition, $Sc(OTf)_3$ was found to be equally as efficient. Intersetingly, $La(OTf)_3$ showed poorer results than LaI_3, whereas $Eu(OTf)_3$ is a better catalyst than $EuCl_3$. In their research, Fukuzawa and Hongo [88] reported that $LaCl_3$ and $LaBr_3$ were less efficient than LaI_3 and that YbI_3 was less efficient than LaI_3. These results suggest that both the nature of the metal centre and the ligands have an important effect on the activity of the catalyst and therefore a good catalyst will contain the optimum compromise between size of the metal cation and electronic properties of the ligands. $Yb(OTf)_3$ was deemed to be the best catalyst for this transformation, as is further supported by its wide ranging utility in organic synthesis. $Yb(OTf)_3$ has been utilised

in the deprotection of methoxyacetates,[91] acetates,[92] and prenyl ethers.[93] The latter of these proceeds *via* initial coordination of Yb to the ethereal oxygen, double bond migration, formation of a carbocation and finally elimination of isoprene to yield the desired alcohol. The deprotection of the acetates proceeds smoothly in the presence of an alcohol to give good yields of the desired esters. These reactions presumably proceed *via* a similar mechanism to that for the methanolysis of *N*-acyl oxazolidinones.

$Yb(OTf)_3$ has also found wide utility as a replacement for more well established Lewis acids due to its interesting properties as a water tolerant, recyclable Lewis acid. Unlike conventional Lewis acids, lanthanides are stable to protic reaction media without loss of Lewis acid capability. Thanks to this, once reaction is complete the catalysts can be easily recovered from the aqueous layer without concomitant loss of activity. These properties have been efficiently exploited by Barrett and co-workers to produce effective catalysts for, amongst others, the acetylation of alcohols,[94] aromatic nitration,[95] and preparation of calix[4]resorcinarenes.[96]

$Yb(OTf)_3$ has also been utilised in the allylation of aldehydes,[97] and as a catalyst for three component coupling reactions in the synthesis of a variety of heterocyclic compounds.[98]

It seems as if $Yb(OTf)_3$ is generally a useful catalyst and is efficient in the methanolysis of *N*-acyl oxazolidinones. Therefore the applicability of this reaction to further substrates was examined.

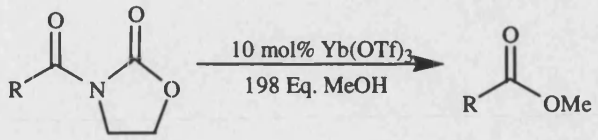
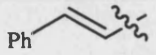
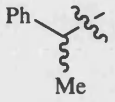
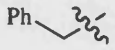
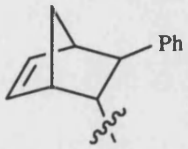
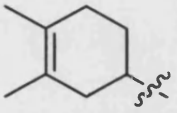


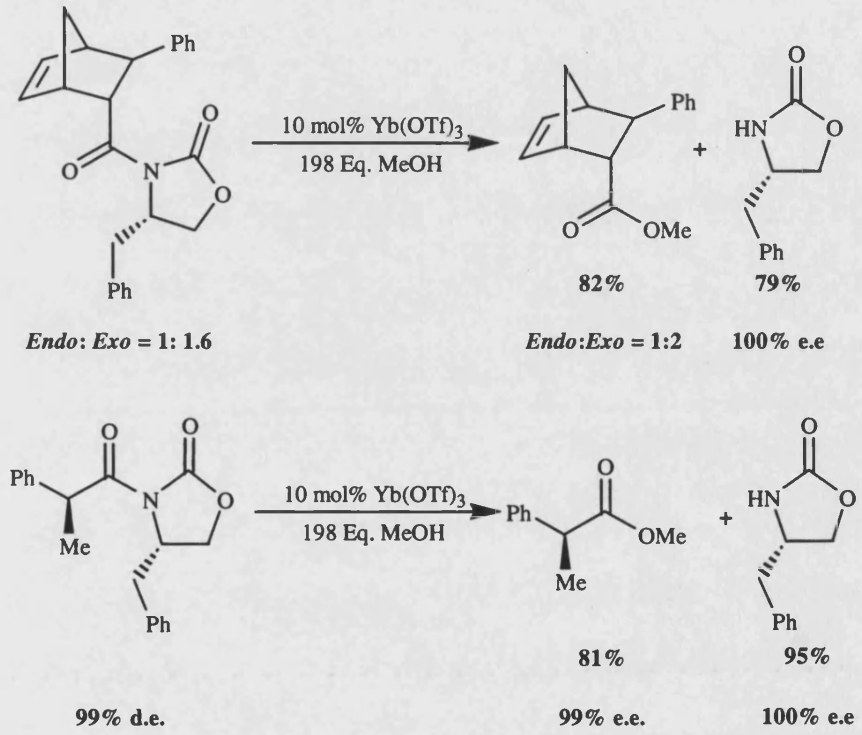
Table 13: Methanolysis of *N*-acyl oxazolidinones

R	Yield
	99%
	92%
	93%
Ph	74%
	99%
	63%

All reactions were routinely left for 17 h before work-up. TLC analysis of the crude reaction mixtures showed that no starting material was left after 1 h for the phenylacetyl and benzoyl derivatives (Entries **3** and **4**), and after 5 h for the cinnamate derivative (Entry **1**). After work-up, conversions were estimated by analysis of the ^{1}H NMR spectra of the crude reaction mixtures, and confirmed by isolating the respective products by column chromatography. All yields quoted in **Table 13** are isolated yields.

$Yb(OTf)_3$ is able to catalyse the methanolysis of a wide range of *N*-acyl oxazolidinone substrates. This methodology appears to be able to tolerate significant steric crowding around the exocyclic carbonyl group but does not lead to any observable endocyclic

cleavage. Methanolysis of the cyclohexene derivative (**Entry 6**) does not proceed to completion within 24 h as judged by ^{1}H NMR analysis. Cleavage of the benzoyl derivative is however complete by analysis of the ^{1}H NMR spectra of the crude reaction mixture, but could not be isolated in greater than 74% yield. No impurities were observed however, suggesting that this is solely an isolation issue. The applicability of this methodology to reagents containing chiral centres was also examined.



Scheme 59

In both cases cleavage occurred with no observed epimerisation of the chiral centres and the desired products could be isolated in good yield. In addition, the oxazolidinone auxiliary can be recovered in good yield and excellent e.e. In the case of the Diels-Alder adduct, a minor impurity could also be isolated, corresponding to an endocyclic cleavage product as ^{1}H NMR analysis clearly shows the appearance of an amido functionality. It is envisaged that this ring opening reaction can be

suppressed by altering concentration or other external parameters and will hopefully prove unimportant.

Of interest is the observed *endo:exo* ratio for the methyl ester Diels-Alder product. When the reaction is run using an auxiliary bearing no asymmetric substituent, an *endo:exo* ratio of 1.8:1 is observed. When an asymmetric substituent is used, the ratio changes to favour formation of the *exo* product. It was envisaged that π-stacking between the alkene and benzyl group may influence the reaction and lead to an enhanced proportion of the *endo* product. However this does not appear to be the case, and either steric effects preclude formation of the *endo* product and favour *exo* formation or π-stacking occurs between the benzyl group and phenyl group of the cinnamate to give a mixture of products depending on the ability to control the position of the phenyl group in the product. In addition, this reaction is not highly stereoselective presumably due to incompatibility of the benzyl oxazolidinone group with the steric needs of the system. Indeed, this particular substrate combination has not been previously reported in the literature, suggesting difficulties in obtaining good selectivity.

It would be useful if other alcohols could be utilised to form more synthetically useful esters. As such, various *N*-acyl oxazolidinone substrates were examined to see if they could be cleaved with either phenol or benzyl alcohol.

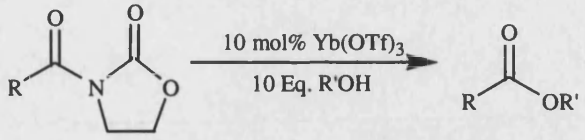
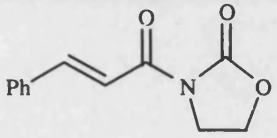
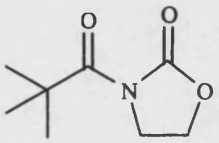
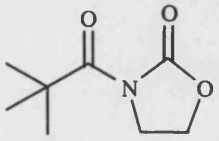
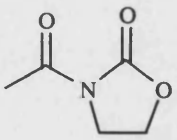
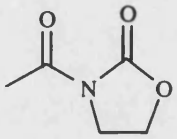
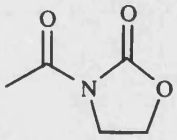


Table 14: Transesterification of various *N*-acyl oxazolidinones

Substrate	Alcohol	Yield
	PhOH	30%[a]
	PhOH	0%[b]
	BnOH	7%[b]
	MeOH	74%[b]
	PhOH	0%[b]
	BnOH	40%[b]

[a]: reaction run at reflux, isolated yield; [b]: conversion determined by GC

The reactions are run in an analogous manner to the methanolysis reactions, although when benzyl alcohol or phenol are used only ten equivalents of alcohol are utilised. In these relatively unhindered cases little conversion into the desired products is observed. As less alcohol is used in these cases, this may not be altogether surprising, however this may suggest that $Yb(OTf)_3$ is not widely applicable to the use of other

alcohols rather methanolysis is the preferred reaction. By using more forcing conditions (**Entry 1**) phenyl cinnamate can be isolated in moderate yield. However, the advantages of using $Yb(OTf)_3$ as a Diels-Alder catalyst in the proposed full cycle helps to circumvent these possible limitations.

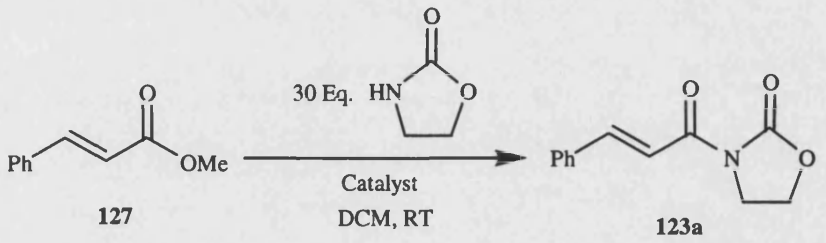
For the proposed full cycle to work, it must be possible to establish an equilibrium between ester and *N*-acyl oxazolidinone substrates. Therefore, the direct conversion of esters into oxazolidinones was examined.

3.3 Conversion of esters into N-acyl oxazolidinones

There are many methods available for the formation of *N*-acyl oxazolidinones, however these mainly utilise acid chlorides or anhydrides as the acyl source and require a strong base to deprotonate the oxazolidinone.[46, 99] Substrates such as carboxylic acids can be transformed into the corresponding oxazolidinones if the leaving group is improved. For instance, various α,β-unsaturated carboxylic acids can be transformed directly into the corresponding *N*-acyl oxazolidinone on treatment with 2-chloro-1-methylpyridinium iodide and a suitable base.[100] These methods tend to cause polymerisation of acryloyl substrates, however this can be overcome by utilising the magnesium salt of the oxazolidinone and the appropriate acid chloride,[101] or the *N*-trimethylsilyl derivative in the presence of copper(II) chloride and copper powder.[102] Alternatively, triethylamine in the presence of either lithium chloride [103] or DMAP [104] also gives good yields for acryloyl derivatives.

There are nevertheless, no suitable methods for directly transforming esters into their *N*-acyl oxazolidinone derivatives. For that reason, the applicability of the $Yb(OTf)_3$ transesterification methodology to this problem was examined. Initially the best

catalysts for carrying out the methanolysis of oxazolidinyl cinnamate **123a** were examined to discover if they could also catalyse the formation of oxazolidinyl cinnamate **123a** from methyl cinnamate **127**.



127 **123a**

Scheme 61

Table 15: Formation of N-acyl oxazolidinone **123a** from methyl cinnamate **127**

Catalyst (mol%)	Yield
LaI_3 (20 mol%)	No Reaction
LaI_3 (100 mol%)	No Reaction
$Yb(OTf)_3$ (10 mol%)	No Reaction
$Sc(OTf)_3$ (10 mol%)	No Reaction
$ZrCl_4$ (10 mol%)	No Reaction

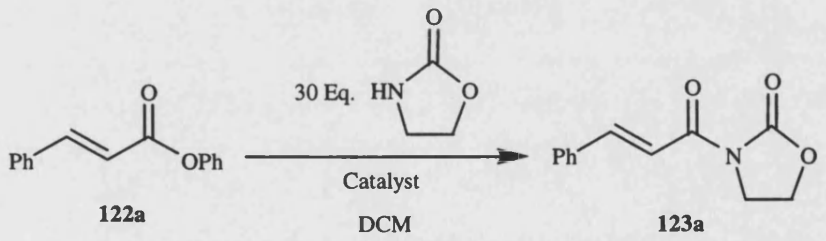
As can be seen, no reaction is observed with any of the catalysts surveyed when 30 Eq. oxazolidinone is used. In these reactions, a precipitate was noticed attributed to the catalyst being relatively insoluble in DCM. Changing to more coordinating solvents such as DMSO and DMF improved the solubility of $Yb(OTf)_3$, however no transesterification was observed. Increasing the reaction temperature so that it was run in DCM at reflux again showed no improvement.

The use of a base to deprotonate oxazolidinone prior to transesterification was attempted. Initial concerns regarding a conjugate addition side reaction proved unsubstantiated, however no transesterification was observed when NaH was used as a base.

The possibility of transesterification occurring between *N*-acyl oxazolidinone substrates and analogous esters was also examined. As such, oxazolidinyl acrylate

119a and methyl cinnamate **127** were treated with 10 mol% LaI_3 and 1 Eq. oxazolidinone. It was hoped that if any crossover did occur, it would be detected by the formation of methyl acrylate **114** and oxazolidinyl cinnamate **123a**. HPLC analysis showed no such crossover transpired.

Methyl esters appear to be relatively inert to any of the transesterification conditions investigated. This is not altogether unsurprising as for the reaction to proceed a methoxide anion must be released. This is not a particularly good leaving group and as such the reaction would be unfavourable. It was envisaged that by changing to a more labile ester the transesterification reaction could be made to proceed. Phenyl esters are known to be more readily labile than alkyl esters and therefore the reaction was examined with these substrates.



122a **123a**

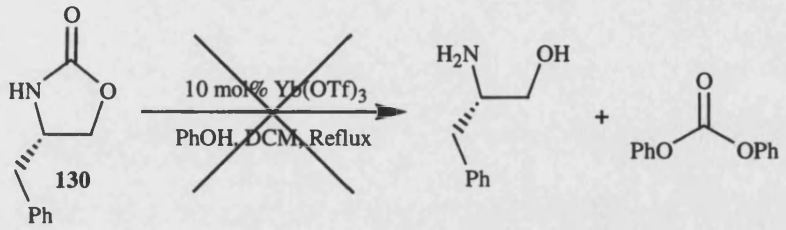
Scheme 62

When this reaction was attempted utilising 10 mol% $Sc(OTf)_3$, 10 mol% $Yb(OTf)_3$, 10 mol% $ZrCl_4$ or 1 Eq. $ZnCl_2$ and 30 Eq. oxazolidinone at room temperature no transesterification was observed. Running the reactions in DCM at reflux showed no change for the $Sc(OTf)_3$, $ZrCl_4$ or $ZnCl_2$ catalysed reaction. However when $Yb(OTf)_3$ was utilised, oxazolidinyl cinnamate **123a** could be isolated in 10% yield after purification by column chromatography. Changing to 1 Eq. oxazolidinone or 10 mol% oxazolidinone slowed the reaction such that no oxazolidinyl cinnamate **123a** could be observed by ^1H NMR analysis.

This low yielding reaction can be considered as a substantial breakthrough. In the proposed cycle, a low conversion into the auxiliary bound substrate should push the cycle towards completion. When the auxiliary bound substrate is produced it undergoes the Diels-Alder reaction rapidly. Removal of the auxiliary bound substrate forces the equilibrium to destroy more starting substrate to compensate. The auxiliary bound Diels-Alder adduct also undergoes transesterification to give the desired product. Even though it appears as if the phenolysis of oxazolidinones lies in favour of the starting material, this reaction is simply sluggish. Given a long enough reaction time it is anticipated that good yields of the desired adduct can be obtained utilising these conditions. Interestingly, when a 1:1 mixture of phenyl cinnamate **122a** and oxazolidinyl cinnamate **123a** is subjected to the transesterification conditions (1 Eq. oxazolidinone, 10 mol% $Yb(OTf)_3$, reflux) no change in ratio is observed as determined by ^1H NMR. As no more oxazolidinyl cinnamate **123a** is produced it appears as if crossover is indeed sluggish.

As an alternative, the use of DMAP to catalyse the formation of oxazolidinyl cinnamate **123a** from phenyl cinnamate **122a** was examined. When this reaction was carried out at room temperature with 1 Eq. oxazolidinone and 1 Eq. DMAP, analysis of the crude reaction mixture by TLC showed no oxazolidinyl cinnamate **122a** had been produced. However, when this reaction was carried out in DCM at reflux, oxazolidinyl cinnamate **122a** was isolated, along with phenyl cinnamate **123a** in an amount corresponding to 14% conversion, after column chromatography. However, the use of DMAP as a transesterification catalyst was not examined further due to problems with endocyclic cleavage alluded to earlier.

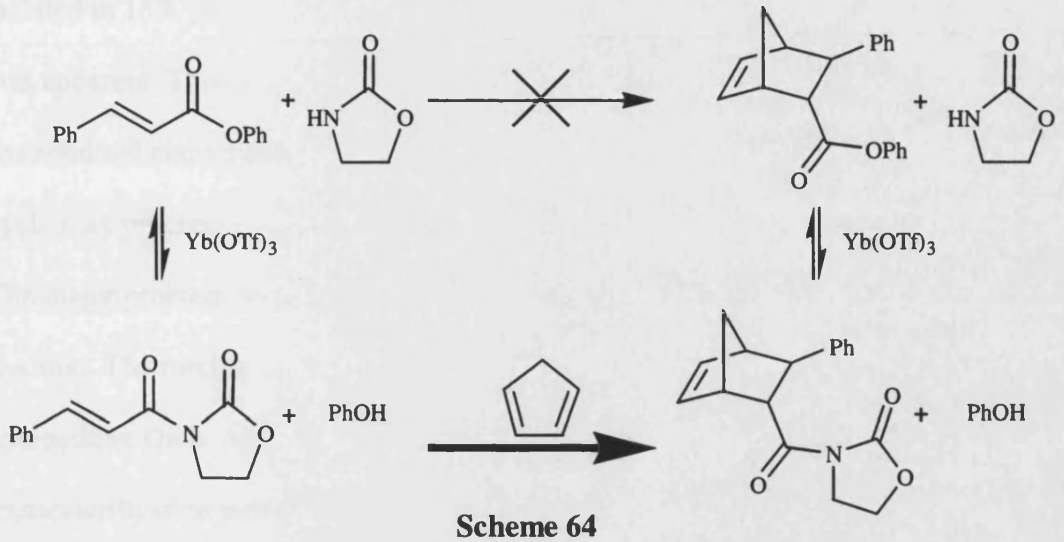
In the proposed full cycle there will be a certain amount of oxazolidinone auxiliary present. If this is destroyed under the reaction conditions the cycle will fail. To confirm its stability, benzyl oxazolidinone **130** was heated at reflux in the presence of PhOH and 10 mol% $Yb(OTf)_3$. If decomposition does occur *via* a ring-opening pathway, diphenylcarbonate and phenylalaninol should be detected. ^1H NMR analysis of the reaction mixture showed only unreacted starting material, suggesting it is stable to the transesterification reaction conditions.



Scheme 63

It has already been shown that phenyl cinnamate **122a** is relatively inert to cycloaddition under the conditions required for transesterification to occur (<5% yield, 10 mol% $Yb(OTf)_3$, DCE, reflux 18 h) whereas oxazolidinyl cinnamate **123a** is far more reactive (>90% yield, 10 mol% $Yb(OTf)_3$, DCM, reflux, 6 h). In light of these results, a full cycle was attempted utilising phenyl cinnamate **122a** as the starting material.

3.4 Attempted catalytic cycle with phenyl cinnamate 122a



Scheme 64

Initial attempts followed the same reaction procedure as used for the transesterification reaction with the extra addition of 5 Eq. cyclopentadiene. When either 1 Eq. or 10 Eq. of oxazolidinone were utilised, no Diels-Alder adducts were observed. In addition, no *N*-acyl oxazolidinone substrates were seen. Two possible reasons for the lack of activity can be postulated. Firstly, when heated under such severe conditions for a prolonged reaction time cyclopentadiene will itself dimerise. This will stop any possible Diels-Alder reaction occurring, and hence any catalytic activity will be diminished. Since no *N*-acyl oxazolidinone substrates are witnessed the transesterification reaction is very slow. This may not be a substantial problem as if even a small amount of oxazolidinyl cinnamate **123a** is produced it should undergo rapid Diels-Alder reaction and force the cycle towards completion.

The reaction was repeated but this time with addition of extra equivalents of cyclopentadiene every 2 h for 10 h and the reaction left at reflux overnight. When 1 Eq. of oxazolidinone is used, the desired product **122c** can be isolated in 11% yield. In addition, phenyl cinnamate can be recovered in an amount corresponding to 13% conversion. It is also possible to carry out an asymmetric version of this reaction. By

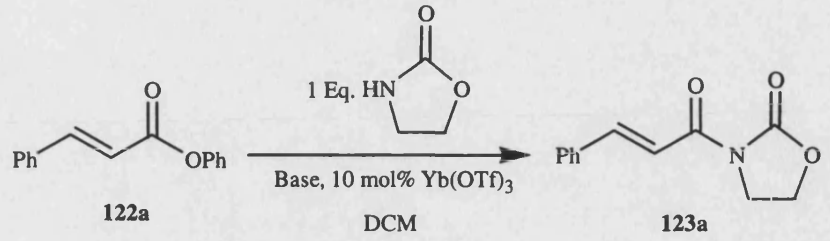
utilising 1 Eq. benzyl oxazolidinone **130**, the desired Diels-Alder adduct **122c** can be isolated in 15% yield. However, under these forcing conditions, no enantioselectivity was apparent. This contradicts the stereoselection seen when the reaction of benzyl oxazolidinyl cinnamate **124** is carried out independently, suggesting a portion of the cycle may proceed via the non-catalysed pathway.

The major problem with this methodology appears to be the slow transesterification reaction. The forcing conditions required make obtaining good rates between the competitive Diels-Alder reactions hard to accomplish. As such milder methods for the transesterification were sought.

3.5 Transesterification with deprotonated oxazolidinones

One reason for the low yield of cleavage when utilising oxazolidinone can be attributed to its low nucleophilic nature. This can be improved by forming the anion on treatment with a suitable base. As shown previously, the attempted cleavage of methyl cinnamate **127** with sodium oxazolidinone was not possible. However, as the amount of conversion using the neutral auxiliary was improved by changing to the more labile phenyl esters, it was hoped that the cleavage of phenyl esters by deprotonated oxazolidinone would be a facile process.

The effect of different bases on the cleavage of phenyl cinnamate **122a** using 1 Eq. deprotonated oxazolidinone was examined. All products were isolated by column chromatography and their identity confirmed by ^{1}H NMR analysis.



122a 123a

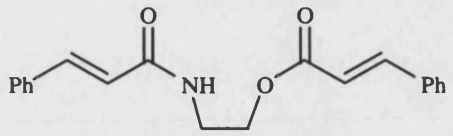
Scheme 65

Table 16: Transesterification utilising deprotonated oxazolidinone

Base	Isolated Yield	Conversion[a]
NaH	31%	82%
BuLi	38%	67%

[a]: conversion based on consumed starting material

Both bases enable a good amount of oxazolidinyl cinnamate **123a** to be isolated even though only 1 Eq. oxazolidinone was used. These results compare very favourably to those obtained when neutral oxazolidinone is used (10% isolated yield, 10 mol% $Yb(OTf)_3$, DCM, reflux) . This confirms the belief that deprotonation of the oxazolidinone will increase its ability to undergo transesterification. However, the isolated yield does not correspond to the conversion obtained by consumed starting material. This discrepancy can be accounted for in two ways. Firstly, an impurity is also isolated. ^1H NMR and mass spectroscopic analysis confirm its identity to be that of "dimeric" species **131**. In a similar manner to the DMAP catalysed methanolysis of oxazolidinyl cinnamate **123a** to form methyl ether **128**, it appears as if endocyclic cleavage of the oxazolidinone ring has occurred, followed by acylation of the resultant alcohol functionality. Again, it is hoped that changing the concentration of the reaction or moving to a more sterically hindered auxiliary can suppress the formation of this dimer. This accounts for a majority of the missing mass balance, however not all. The rest may be accounted for as phenyl cinnamate **122a** decomposes to a small degree during chromatography. However, since greater than 30% of the desired product can be isolated this is a minor point.



131

Scheme 66

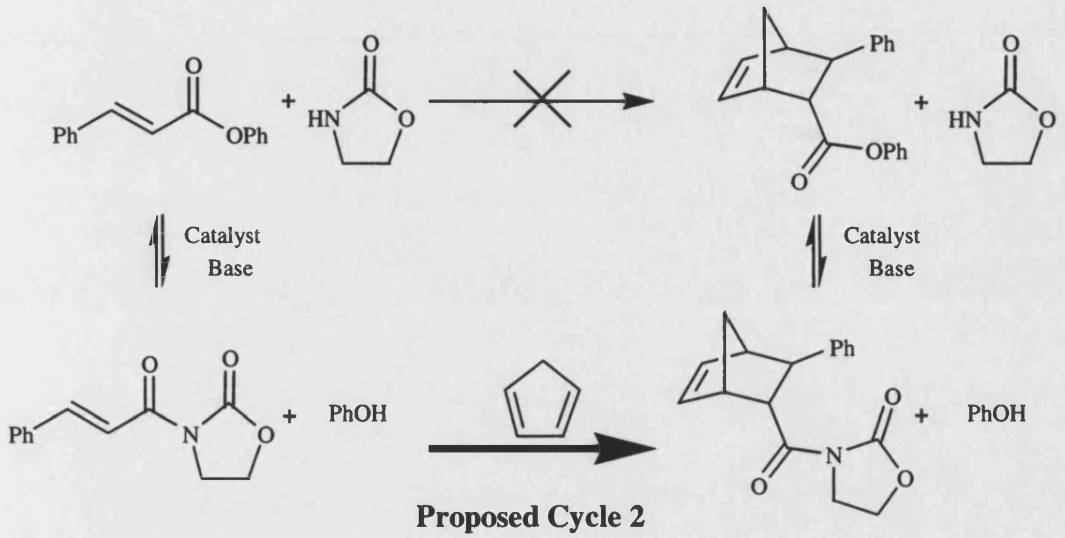
This reaction can also be run in reverse, i.e. cleavage of oxazolidinyl cinnamate **123a** using 1 Eq. PhOH, 10 mol% $Yb(OTf)_3$ and a suitable base. Phenyl cinnamate **122a** can be isolated in 14% yield (80% conversion) when NaH is used, or at 21% conversion when BuLi is used. In the latter case, too small an amount of phenyl cinnamate was produced to isolate by chromatography. In both cases, the "dimeric" species **131** could also be isolated.

Since the deprotonated oxazolidinone appears to be an efficient nucleophile, the need for $Yb(OTf)_3$ to be present during the transesterification reaction was examined. Indeed, the reaction does proceed without the need for added catalyst. When NaH is used as a base, oxazolidinyl cinnamate **123a** can be isolated in 54% yield (83% conversion based on consumed starting material). Again, dimer **131** can be isolated as confirmed by ^1H NMR analysis. This reaction can also be carried out at 0 °C, giving oxazolidinyl cinnamate in 25% isolated yield (76% conversion). When BuLi is used as the base at 0 °C, oxazolidinyl cinnamate **123a** can be isolated in 20% yield (42% conversion). The reverse transformation of oxazolidinyl cinnamate **123a** into phenyl cinnamate **122a** using metal phenoxide was also examined. When NaH is used as a base, phenyl cinnamate **122a** can be isolated in 10% yield (49% conversion) whereas the use of BuLi as a base allows isolation of the product in 15% yield (49% conversion). Using either DBU or potassium carbonate gave no reaction.

Alternatively, when the reaction is carried out at 0 °C, NaH gives the product in 4% yield (34% conversion) however BuLi shows no reaction.

It appears as if oxazolidinyl cinnamate is being destroyed under the reaction conditions by a process that competes with the desired transesterification reaction. To test the relative rates of these reactions oxazolidinyl cinnamate **123a** was reacted with sodium phenoxide in the presence of 10 mol% phenyl cinnamate **122a**. After 6 h, when very little transesterification should have taken place, ^{1}H NMR analysis showed the reaction mixture contained 12% phenyl cinnamate **122a** relative to oxazolidinyl cinnamate **123a**. Peaks corresponding to PhOH, or possibly diphenyl carbonate could also be observed. The dimeric impurity **131** however, could not be resolved by ^{1}H NMR analysis. After chromatography, phenyl cinnamate was isolated in 10% yield, corresponding to no reaction. The recovered amounts of PhOH and oxazolidinyl cinnamate **123a** corresponded to 35% conversion. The amount of dimeric impurity **131** isolated amounted to 6% of the reacted oxazolidinyl cinnamate. This suggests other impurities are in existence that cannot be isolated, presumably due to the small amounts present. However, a reasonable method for transesterification appears to have been developed and as such, attempts were made to adapt this methodology to the development of the proposed catalytic cycle.

3.6 Catalytic cycle utilising deprotonated auxiliary transesterification



Proposed Cycle 2

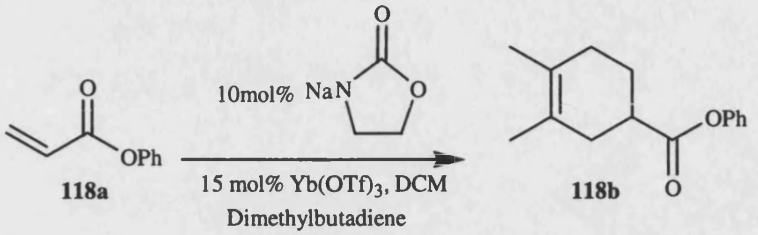
Attempts were made to obtain a full catalytic cycle using the same reaction conditions as found for the transesterification reaction. The reaction of phenyl cinnamate **122a** with cyclopentadiene using deprotonated oxazolidinone was examined. Initially, the effect of different Lewis acids on the full cycle was examined.

When 10 mol% $Cu(OTf)_2$ was used as a catalyst under standard conditions (1 Eq. oxazolidinone, 1.1 Eq. NaH, DCM, RT), no Diels-Alder adducts could be isolated or observed by TLC or ^1H NMR analysis. Oxazolidinyl cinnamate **123a** could be isolated in 24% yield, PhOH was isolated in 84% yield, and phenyl cinnamate **122a** could be re-isolated in an amount corresponding to 76% conversion after column chromatography. In comparison, when the reaction was run with no added oxazolidinone, only starting material was observed. This suggests that the cycle does proceed as oxazolidinyl cinnamate **123a** can be isolated, however since no Diels-Alder reaction occurs a stronger Lewis acid was used. The reaction was run using 10 mol% $TiCl_4$ as a catalyst and in the blank reaction where no chiral auxiliary is used, no starting phenyl cinnamate **122a** or products can be observed by TLC. It appears as

if the strong titanium Lewis acid has destroyed all adducts present. When the reaction is run under standard cycle conditions (1 Eq. oxazolidinone, 1.1 Eq. NaH, DCM, RT), phenyl cinnamate **122a** is recovered in an amount corresponding to 33% conversion, and PhOH isolated in 36% yield after column chromatography. The remaining mass balance was isolated and ^{1}H NMR analysis suggests the product is some type of Diels-Alder adduct, although its exact identity has not been established.

Changing the catalyst to $Sc(OTf)_3$ again showed some interesting results. In the blank reaction where no oxazolidinone is used, the reaction polymerises after work-up resulting in a brown polymeric material that could not be redissolved in any solvent. However when the reaction is run in the presence of deprotonated oxazolidinone, work-up proceeds as expected to give an oil which upon purification by column chromatography allows oxazolidinyl cinnamate **123a** to be isolated in 27% yield, PhOH in 89% yield and phenyl cinnamate **122a** can be re-isolated in an amount corresponding to 79% conversion. In addition the dimeric by-product **131** can be isolated in an amount that corresponds to 7% of the missing cinnamate substrate. It seems as if addition of the oxazolidinone has altered the activity of the Lewis acid. No Diels-Alder adducts can be observed by analysis of the ^{1}H NMR of the crude reaction mixture. If the use of cyclopentadiene may be a problem, the less reactive 2,3-dimethyl-1,3-butadiene was used with phenyl acrylate **118a** in the presence of 10 mol% $Sc(OTf)_3$. When no oxazolidinone is used, the desired Diels-Alder adduct **118b** was isolated in 17% yield after column chromatography. However, when 1 Eq. of oxazolidinone is used with sodium hydride as the base, no Diels-Alder adduct can be observed by ^{1}H NMR analysis.

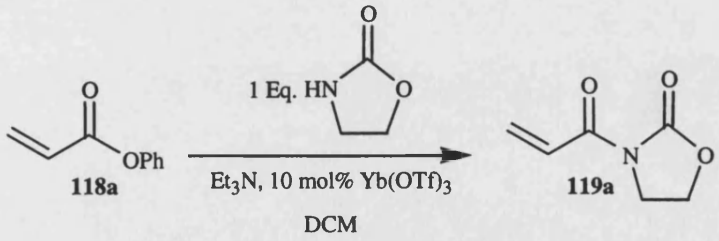
It appears as if the use of oxazolidinone deprotonated by sodium hydride interacts with the Lewis acid present to reduce its Lewis acidity thereby making it inactive in the Diels-Alder reaction. To see if this can be circumvented more Lewis acid than deprotonated auxiliary was used.



Scheme 67

In the blank reaction with no oxazolidinone present, analysis of the crude reaction mixture by TLC showed only starting phenyl ester **118a**, however in contrast the reaction with 10 mol% deprotonated auxiliary showed the formation of oxazolidinyl acrylate **119a**, but no Diels-Alder adduct was observed. Addition of extra portions of $Yb(OTf)_3$ did not aid the production of any Diels-Alder adducts. This supports the hypothesis that the Lewis acid and base present interact in an unfavourable manner to slow any Diels-Alder reaction, therefore retarding the full cycle.

The use of the organic base triethylamine was examined to see if this was suitable for the transesterification of phenyl acrylate **118a** with oxazolidinone.

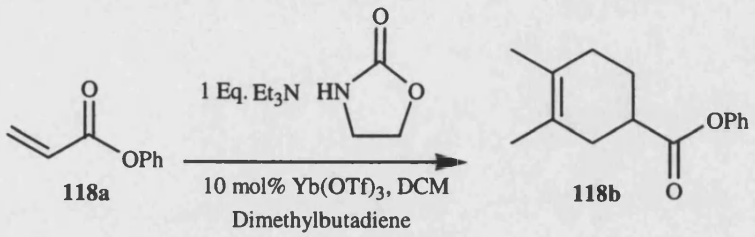


Scheme 68

Transesterification is possible utilising triethylamine as a base to give oxazolidinyl acrylate **119a** in 3% isolated yield and PhOH in 6% yield. In addition, 78% of the starting phenyl acrylate **118a** can be recovered. Analysis of the ^1H NMR of the crude

reaction mixture showed 18% conversion into the desired product acrylate **119a**. This suggests that triethylamine can be used as a base for the transesterification reaction and as such, its utility for the proposed full cycle was examined.

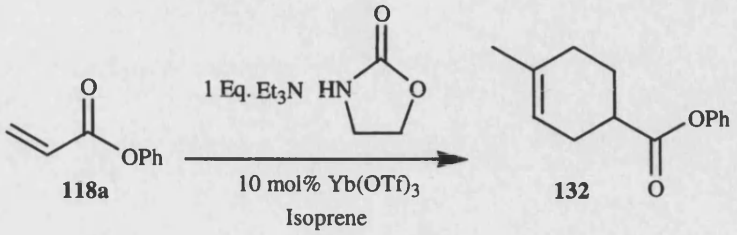
3.7 Full catalytic cycle utilising triethylamine



Scheme 69

When the full cycle is attempted utilising 1 Eq. oxazolidinone deprotonated with triethylamine and 10 mol% $Yb(OTf)_3$, TLC analysis of the crude reaction mixture shows production of oxazolidinyl acrylate **119a**, but no Diels-Alder reaction. As expected, the blank competition reaction where no oxazolidinone is used shows no reaction. Since no Diels-Alder reaction has occurred when it is expected that under these conditions oxazolidinyl acrylate **119a** should undergo cycloaddition to give the Diels-Alder adduct **119b** in very good yield (100% yield 18 h). It appears as if the base interacts with the Lewis acid in such a way as to deactivate it, rendering it a poor catalyst for the Diels-Alder reaction. This is in close analogy with results obtained by Kobayashi in his research towards an ytterbium catalyst for asymmetric Diels-Alder reactions.[85c] An efficient catalyst is obtained when $Yb(OTf)_3$, (*R*)-(+)-binaphthol and *cis*-1,2,6-trimethylpiperidine are used in conjunction. However, if (*R*)-(+)-binaphthol is not used in the preparation of the catalyst, it becomes inactive due to coordination of the amine to the $Yb(OTf)_3$ to decrease its activity.

Hence, the rate of Diels-Alder reaction has been decreased remarkably when deprotonated auxiliary is present. To try and overcome this, the reaction temperature was increased to enhance the rate of cycloaddition.



Scheme 70

Initially, the proposed cycle outlined in **Scheme 70** was run, and the reaction carried out in neat isoprene at reflux in a sealed pressure tube. In both cases, ^{1}H NMR analysis showed no acrylate peaks suggesting both reactions have proceeded to complete conversion. The background rate of cycloaddition therefore needs to be lowered before the cycle can be made to proceed successfully.

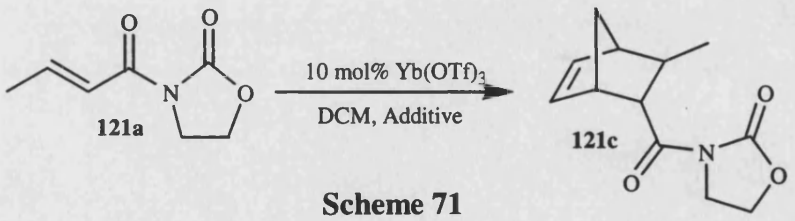
In an attempt to achieve this aim, the same reaction was run utilising DCM as a solvent at reflux in a sealed pressure tube. ^{1}H NMR analysis of the crude reaction mixture showed that when no auxiliary is added, the reaction proceeds to 41% conversion. When deprotonated oxazolidinone is used, ^{1}H NMR analysis shows that phenyl acrylate **118a** has been transformed into the three possible products in 71% conversion. ^{1}H NMR analysis shows that phenyl acrylate **118a** has been converted to the Diels-Alder adducts in 68% conversion. In addition, transformation to the corresponding oxazolidinyl acrylate **119a** occurs in 30% conversion. This again shows that the proposed cycle does proceed, however, the background rate of reaction is still far too high. As such, various changes to the conditions were made to see if this could be altered.

The reaction between phenyl acrylate **118a** and 2,3-dimethylbutadiene, shown in **Scheme 69**, was run at different temperatures in a pressure tube and the various conversions determined by analysis of the ^{1}H NMR of the crude reaction mixtures.

Table 17: **Scheme 69** run at various temperatures

Conversion type	Conversion at 35 °C	Conversion at 85 °C
118a to **118b**	27%	89%
118a to **119a**	37%	26%
118a to all	87%	94%
Blank **118a** to **118b**	11%	79%

The reaction was also attempted using the less reactive dienophile phenyl cinnamate **122a** and the reactive cyclopentadiene in a pressure tube at reflux (oil bath 75 °C). Analysis of the crude ^{1}H NMR was difficult in this case due the complexity of the Diels-Alder adducts, however column chromatography allowed isolation of the phenyl esters. In the blank reaction conversion of phenyl cinnamate **122a** into the Diels-Alder adduct **122c** was 15%. When deprotonated auxiliary is used, the conversion increases to 30%. In addition, the oxazolidinone substrates are also present in the reaction mixture so the overall conversion of phenyl cinnamate **122a** is higher. In all cases it appears as if the presence of the deprotonated oxazolidinone is retarding the rate of Diels-Alder reaction. Attempts were made to determine exactly what was causing this effect using the Diels-Alder reaction of oxazolidinyl crotonate **121a** as a model.



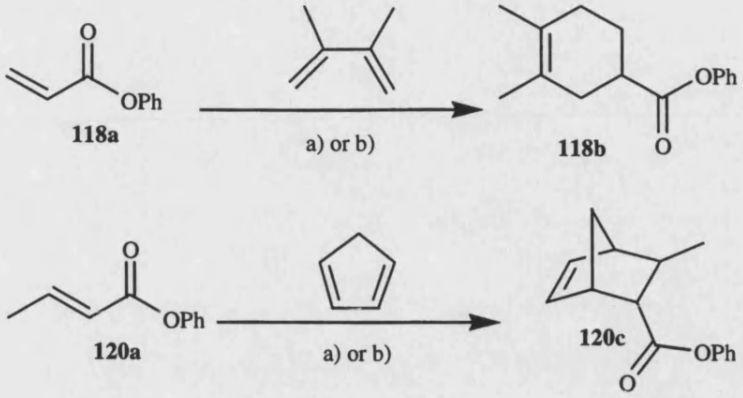
Scheme 71

Table 18: Effect of various additives on the Diels-Alder reaction of **121a**

Additive	Conversion
None	100%
Oxazolidinone	91%
Et_3N	11%
Oxazolidinone and Et_3N	18%

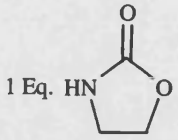
The effect of different additives on the Diels-Alder reaction of **121a** with cyclopentadiene was determined by ^{1}H NMR analysis of the isolated *N*-acyl oxazolidinone substrates. When no additive is used, conversion is excellent, with no starting crotonate **121a** present. Addition of 1 Eq. oxazolidinone retards the reaction slightly, although the conversion is still excellent. However, by addition of triethylamine the rate of reaction is retarded considerably. In both cases it appears as if the amine coordinates to the $Yb(OTf)_3$ decreasing its Lewis acidity. This effect is particularly pronounced for the tertiary triethylamine. However, as the lone pair of electrons on nitrogen in oxazolidinone is also delocalised into the adjacent carbonyl group it is less available to bind to the metal centre, making it less deactivating.

Since the Lewis acidity of $Yb(OTf)_3$ is modified in the presence of triethylamine, the reaction used as a blank background comparison may be considered an unfair estimate of the underlying rate of Diels-Alder reaction for the starting substrate. As such, full cycles were attempted where the competition reaction had 1 Eq. triethylamine added to reduce the Lewis acidity of $Yb(OTf)_3$, making it a fairer comparison.



a) 1 Eq. Et_3N, 10 mol% $Yb(OTf)_3$, DCM

b) 1 Eq. Et_3N, 10 mol% $Yb(OTf)_3$, DCM



Scheme 72

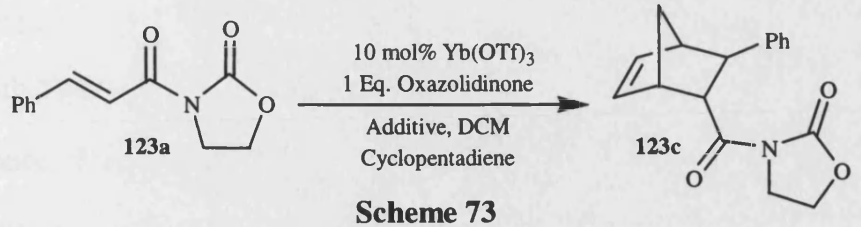
When the reaction of phenyl acrylate **118a** is run in the presence of 10 mol% $Yb(OTf)_3$ and 1 Eq. triethylamine in DCM at 65 °C in a sealed pressure tube, the cycloadduct **118b** is produced in 35% conversion as determined by analysis of the ^1H NMR of the isolated phenyl ester adducts. When 1 Eq. oxazolidinone is added to the cycle under analogous conditions, conversions determined by ^1H NMR analysis showed that phenyl acrylate **118a** was converted into its cycloadduct **118b** in 57% conversion. Conversion of phenyl acrylate **118a** to both phenyl and oxazolidinyl cycloadducts **118b** and **119b** proceeds in 68% conversion and conversion between phenyl acrylate **118a** and oxazolidinyl acrylate **119a** proceeds in 24% conversion. Overall, this suggests that 71% of the starting phenyl acrylate has been consumed. Changing to the reaction between the less reactive phenyl crotonate **120a** and cyclopentadiene made interpretation of the crude ^1H NMR difficult due to the complexity of the cycloadducts. However, after column chromatography conversion of phenyl crotonate **120a** into cycloadduct **120c** was deemed to proceed with 22%

conversion when no oxazolidinone is used, and in 32% conversion with oxazolidinone present. In both cases, addition of oxazolidinone to the reaction makes the overall consumption of starting material increase relative to that when no auxiliary is present. However, in both cases there is a substantial background Diels-Alder reaction taking place, meaning attempts at producing a enantioselective version of this cycle will be limited until this can be reduced. Ways to overcome the deactivation of the Lewis acid by added base were examined so as to be able to re-establish the good rate differences obtained previously between the Diels-Alder reactions of starting and auxiliary bound substrates.

3.8 Overcoming Lewis acid deactivation by various bases

To see if steric effects could be used to overcome the deactivation of $Yb(OTf)_3$, the Diels-Alder reaction of oxazolidinyl crotonate **121a** with cyclopentadiene was run in the presence of 1 Eq. oxazolidinone and 1.01 Eq. diisopropylethylamine (Hünig's base). ^1H NMR analysis of the crude reaction mixture showed that the Diels-Alder reaction proceeded in less than 15% conversion, in fact the cycloadduct **121c** was only just visible by ^1H NMR analysis whereas when no base is used quantitative yields can be achieved.

At this stage it was discovered that better resolution of the ^1H NMR could be achieved by swapping to the oxazolidinyl cinnamate dienophile **123a**. This reaction was examined in the presence of various bases to see their effect on the rate of cycloaddition, which usually proceeds to give cycloadduct **123c** in 97% yield in the absence of any base.



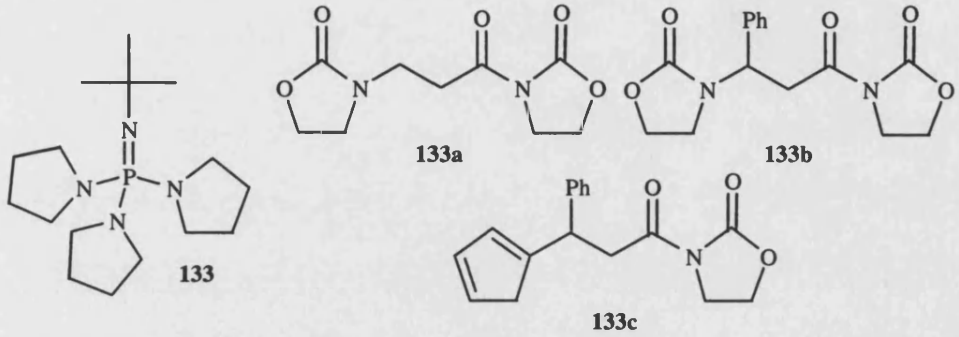
Scheme 73

The hindered bases 1,2,2,6,6-pentamethylpiperidine, DBU and DABCO showed no formation of the desired cycloadduct **123c** by analysis of the ^{1}H NMR of the crude reaction mixtures. DMAP and CsF were also surveyed, but again showed no conversion to the desired product by ^{1}H NMR analysis. Since the Diels-Alder reaction was retarded, the effect of adding an extra Lewis acid to promote the cycloaddition reaction was examined by carrying out the reaction in the presence of 1 Eq. triethylamine and 10 mol% $Cu(OTf)_2$. Unfortunately, no Diels-Alder adduct was observed by analysis of the crude ^{1}H NMR.

Various lanthanide triflates have been solubilised by the addition of polyether and poly(ethylene glycol) additives.[105] These coordinate to the metal centre to give active Diels-Alder catalysts. Since addition of the base causes a precipitate to appear, one possible reason for the lack of activity could be attributed to the insolubility of the resultant ytterbium complex. As such, attempts were made to solubilise this complex by addition of either 1,4-butanediol or 2-methoxyethyl ether (diglyme). Unfortunately neither of these catalysts was active in the Diels-Alder reaction. Both appeared soluble, but on addition of triethylamine the reaction containing 1,4-butanediol instantly turned cloudy suggesting formation of a Yb/amine complex. By comparison the reaction containing diglyme was more soluble, but still showed some precipitate. Addition of cyclopentadiene resulted in more precipitate being formed in both cases. As such it appears that the addition of alcohol or glycol substrates does not solubilise the ytterbium complex formed.

Strong organic bases were also examined to see if they had a similar coordinating effect with $Yb(OTf)_3$. Phosphazene Base P1-t-Bu-tris(tetramethylene) **133** was used in the presence of 10 mol% $Yb(OTf)_3$ and 1 Eq. oxazolidinone to see if it retards the cycloaddition of **123a** with cyclopentadiene. When this reaction is run, no starting material is observed by TLC analysis of the crude reaction mixture after 1 h. However, no Diels-Alder adduct is observed but an unknown impurity is isolated. This impurity is also formed when the reaction is run in the absence of $Yb(OTf)_3$, or if the solvent is changed to MeCN from DCM. This latter alteration suggests that the impurity formation does not proceed *via* a carbene pathway. Alternatively, if the substrate is changed to phenyl acrylate **119a** and the diene to 2,3-dimethylbutadiene, a new side product is observed. These results suggest that conjugate addition may be responsible for the formation of the by-products. ^1H NMR analysis of the impurity from the oxazolidinyl acrylate **119a** reaction suggests that oxazolidinone had added in a 1,4-manner to the acrylate, resulting in formation of the adduct **133a**. Phosphazene base P1 has a high pKa value (pKa≈ 16 of its conjugate acid) and is strong enough to deprotonate cyclopentadiene (pKa≈ 15) enabling it to act as a nucleophile rather than a diene.[125] In addition, since the phosphazene base P1/oxazolidinone adduct is soluble in organic solvents unlike the corresponding alkali metal salts, conjugate addition reactions occur more readily. Hence, the reaction of oxazolidinyl cinnamate **123a** in the presence of oxazolidinone and cyclopentadiene and P1 base could result in the formation of two products; adduct **133b** from the conjugate addition of oxazolidinone and adduct **133c** from the conjugate addition of the aromatic cyclopentadienyl anion with simultaneous rearrangement of the double bonds. If oxazolidinyl cinnamate **123a** is treated solely with the anion of cyclopentadiene, good conversion to the proposed Micheal adduct **133c** is observed. Indeed, analysis of the

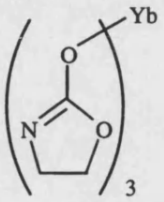
^{1}H NMR spectra and comparision with that of the unknown adduct suggests that this is the sole product obtained from the reaction where both cyclopentadiene and oxazolidinone are present. This is confirmed as analysis of the crude ^{1}H NMR of the reaction between oxazolidinone and oxazolidinyl cinnamate **123a** in the presence of P1 base shows mainly starting material, suggesting that the cyclopentadienyl anion is a more efficient nucleophile than oxazolidinone.



Scheme 73a

Attempts were made to isolate the proposed complex formed between $Yb(OTf)_3$, base and oxazolidinone. Since a variety of bases, including sodium salts, show a similar deactivation effect, it was proposed that the actual complex present might be formed by the reaction of the deprotonated oxazolidinone and ytterbium. Since triethylamine ($pKa= 9.0_{DMSO}$ of its conjugate acid) is not a strong enough base to deprotonate oxazolidinone ($pKa= 24.1_{DMSO}$), it seems as if prior coordination between oxazolidinone and $Yb(OTf)_3$ activates it towards deprotonation. This would result in formation of an oxazolidinyl ytterbium complex **134**. Lanthanide salts are known to be highly oxophilic and difficult to obtain in an anhydrous state, suggesting any complex present would prefer to coordinate to an oxygen anion rather than a nitrogen anion. Therefore, even if ytterbium initially coordinates to the nitrogen of oxazolidinone, it will rapidly isomerise to bind to the oxygen atom.

This complex was synthesised by first deprotonating oxazolidinone with sodium hydride to minimise any other counterions that could be present. Addition of oxazolidinone and separation of the salt produced enabled isolation of the proposed complex **134**. This complex is highly insoluble in any solvent, apart from aqueous acid and as such, no NMR analysis of the product was possible.



134

Scheme 74

The use of this catalyst ($Yb(Ox)_3$) in both transesterification and Diels-Alder reactions was examined. Attempted formation of oxazolidinyl cinnamate **123a** from phenyl cinnamate **122a** showed no transesterification after 72 h. This is not overly surprising since $Yb(OTf)_3$ was not required to catalyse the reaction and, in fact, when it is used the observed yield is lowered. For instance the same crossover when carried out in the presence of $Yb(OTf)_3$ gave oxazolidinyl cinnamate **123a** in 31% yield compared to 54% yield when no lanthanide is present. These results can be explained if it is assumed that some of the oxazolidinone is being removed from the reaction *via* complexation with $Yb(OTf)_3$ therefore reducing the observed yield of oxazolidinyl cinnamate **123a**.

The Diels-Alder reaction of oxazolidinyl cinnamate **123a** with cyclopentadiene to give the cycloadduct **123c** was also examined using $Yb(Ox)_3$. This reaction proceeds with 8% conversion as judged by ^1H NMR analysis of the crude reaction mixture. This is a comparable amount to that observed when the catalyst is prepared *in situ* (18%), suggesting that the prepared catalyst could be responsible for the retarding of the full cycle. The fact that any cycloaddition occurs at all confirms the belief that a

Ytterbium complex has been produced since when the reaction is carried out in the absence of any Lewis acid, no reaction occurs.

3.9 Conclusion

The use of catalytic chiral auxiliaries to promote the Diels-Alder reaction of phenyl esters has been attempted. Each step of the proposed cycle has been proved individually. The use of $Yb(OTf)_3$ has been shown to catalyse the formation of phenyl and methyl esters from a range of corresponding *N*-acyl oxazolidinones. Likewise the *N*-acyl oxazolidinone can be produced from the corresponding phenyl esters utilising a deprotonated auxiliary. Good rate differences can be obtained between a range of α,β-unsaturated phenyl esters and the analogous oxazolidinone substrates utilising $Yb(OTf)_3$ as a catalyst.

However, when these reactions are combined to produce a cycle whereby chiral auxiliaries can be utilised in a catalytic manner, the deprotonated oxazolidinone required for the transesterification reaction interacts with the $Yb(OTf)_3$, reducing its Lewis acidity. This causes the Diels-Alder reaction to be retarded making the cycle inoperable. When the palladium catalysed allylic substitution reaction was used as a method for forming esters from carboxylates, the cycle again failed due to the formation of a palladium-diene complex. In both cases incompatibility of two reagents has caused the cycle to fail.

Similar incompatibility problems were encountered in an attempt to carry out tandem allylic isomerisation and ring-closing metathesis using palladium(0) phosphine and ruthenium benzylidenes as catalysts.[106] In isolation, both allylic substitution and ring-closing metathesis proceed smoothly. However, when both catalysts are used in conjunction tricyclohexylphosphine liberated from Grubbs catalyst coordinates

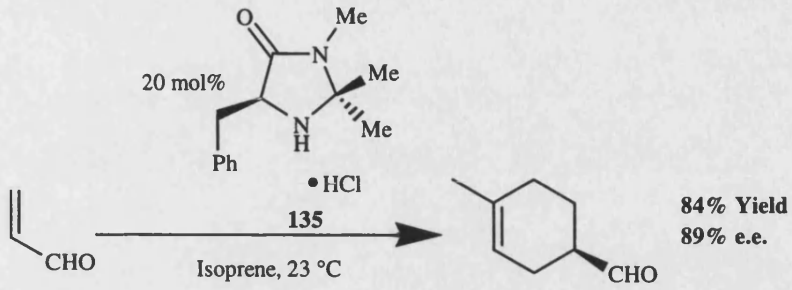
preferentially with palladium, even in the presence of triphenylphosphine, shutting down the allylic isomerisation due to a memory effect.[107] Changing metathesis catalyst to one recently developed which contains a carbene ligand rather than cyclohexylphosphine allows the cycle to proceed.

Incompatibility between reagents is a problem when trying to develop new synthetic methodology. However, the interaction between acceptors and donors can sometimes be desirable. Indeed, $SiCl_4$ has been shown to be an efficient catalyst for the allylation of aldehydes, but only in the presence of the Lewis basic phosphoramide ligand.[108] In effect, the Lewis acid has been *activated* by the addition of the Lewis base, somewhat in contrast to the deactivation of $Yb(OTf)_3$ by deprotonated oxazolidinone.

Some groups have succeeded in using activating groups in a catalytic manner for the enhancement of rate of Diels-Alder reactions. Yamamoto *et al.* have shown that acyloxyborane can be used as an activating group for the Diels-Alder reaction of carboxylic acids.[109] Addition of a suitable borane to a carboxylic acid results in initial formation of an acyloxyborane, which can then undergo cycloaddition with a range of dienes. Catalytic amounts of borane can be used since facile exchange of the borane occurs between Diels-Alder adduct and unreacted acid. By initial complexation of the borane to an enantiomerically pure tartaric acid ligand, asymmetric Diels-Alder reactions can be obtained, with up to 78% e.e being attained.

The group of MacMillan has developed a very efficient organic catalyst.[110] Mimicking a Lewis acid, addition of amine **135** to an α,β-unsaturated aldehyde causes an equilibrium to be established between the aldehyde and the relatively electron-deficient iminium ion. This undergoes rapid cycloaddition relative to the starting aldehyde, and due to the reversible nature of the iminium formation allows recycling

of the active amine catalyst. This catalyst and its analogues have also been successfully utilised in asymmetric 1,3-dipolar cycloadditions and enantioselective Friedel-Crafts alkylations.



Scheme 75

The approaches outlined for the attempted cycle where chiral auxiliaries can be used in a catalytic manner have thus far proved unsuccessful. The scientific concept of the proposal has been proved successfully, however, some final obstacles remain to be overcome before the cycle itself is operational.

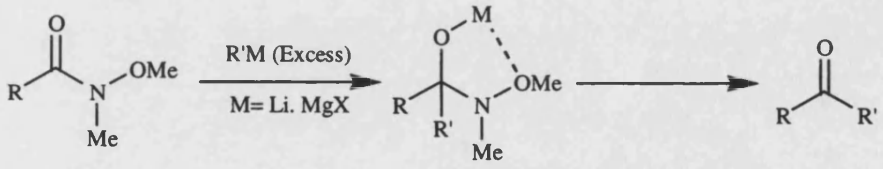
Chapter 4

Impossible Reactions

4) Impossible Reactions

4.1 Weinreb Amides as activating groups

Since the first report by Weinreb on the use of *N*-methoxy-*N*-methylamides **136** in the synthesis of aldehydes and ketones,[111] Weinreb amides have become increasingly popular in organic synthesis.[112] Most reactions however centre on the high stability of the tetrahedral intermediate **137** formed when a Weinreb amide undergoes nucleophilic attack by an organometallic reagent. No overaddition occurs due to effective chelation of metal counterion between carbonyl oxygen and *N*-methoxy oxygen that prevents the collapse of the tetrahedral intermediate until aqueous acidic work-up.

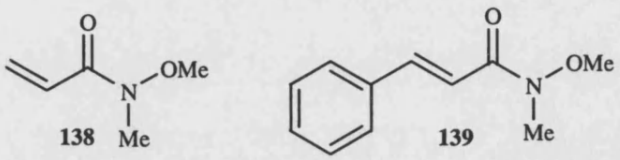


136 **137**

Scheme 76

α,β-Unsaturated Weinreb amides have thus far received relatively little attention in the literature. Although they can be routinely prepared by treatment of the requisite acid chloride with *N*-methoxy-*N*-methylamine hydrochloride and pyridine, Wittig olefination has found applicability particularly for base sensitive substrates.[113] Apart from transformation into the corresponding aldehydes, the reactions of α,β-unsaturated Weinreb amides has been limited to dihydroxylation.[114] As reported by Sharpless, these amides react sluggishly requiring a five-fold increase in the amount of ligand and potassium osmate concentration relative to that required for esters.

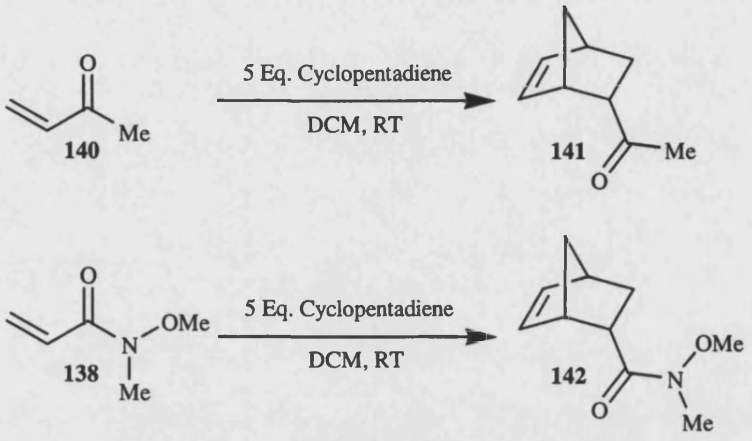
If Weinreb amides are to be considered as an activating group for the proposed catalytic cycle, the Diels-Alder reaction for these substrates must be examined.[150] Weinreb acrylamide **138** and Weinreb cinnamide **139** were prepared from their corresponding acid chlorides according to the procedure originally described by Weinreb. Weinreb cinnamide **139** could be isolated analytically pure and in excellent yield after work-up. However, the more reactive acrylamide **138** requires the resultant oil produced after work-up to be filtered through a pad of silica. This adduct must also be treated carefully when solvent is removed *in vacuo* due to its high volatility.



Scheme 77

The thermal Diels-Alder reaction of methyl vinyl ketone **140** and cyclopentadiene proceeds very rapidly to give >95% conversion in 18 h. Methyl vinyl ketone can be considered a useful analogy for Weinreb acrylamide **138** as simply treating the Weinreb cycloadduct **142** with MeMgBr will generate the methyl ketone Diels-Alder adduct **141**. In comparison, the thermal Diels-Alder reaction of Weinreb acrylamide **138** with cyclopentadiene shows a large amount of starting material remaining after 18 hours. This is not altogether surprising as the amide functional group is a poor electron-withdrawing group. The lone pair of electrons on nitrogen is conjugated with the carbonyl group reducing its electron-withdrawing ability and hence lowering the reactivity of the dienophile towards reaction. Indeed, there are only a few examples of cycloaddition reactions of amide derivatives and these require some method of activation before reaction. For instance, allyl amides are, as anticipated, relatively unreactive. However, cycloaddition can be made to proceed by treating the allyl amine

with two equivalents of iodine.[115] Iodolactonisation forms a cationic cyclic intermediate that readily undergoes cycloaddition reactions. Alternatively, Lewis acids can be utilised to accelerate the Diels-Alder reactions of other acrylamide derivatives.



Scheme 78

It was proposed that the utilisation of a Lewis acid may accelerate the rate of cycloaddition for α,β-unsaturated Weinreb amides. Coordination of the metal to the carbonyl group will enhance the electron-withdrawing nature of the dienophile. In addition further coordination to the *N*-methoxy oxygen, as observed in the tetrahedral reduction intermediate **137**, should give a relatively stable intermediate analogous to those formed when *N*-acyl oxazolidinones are treated with Lewis acids. This would enable either a new chiral auxiliary to be developed by altering the nature of the *N*-alkyl group, or more attractively the stable intermediate formed will enable the use of enantiomerically pure ligands in conjunction with the Lewis acid to develop an asymmetric Diels-Alder reaction. As such, various Lewis acids at the 10 mol% level were examined for their effect on the Diels-Alder reaction of acrylamide **138**.

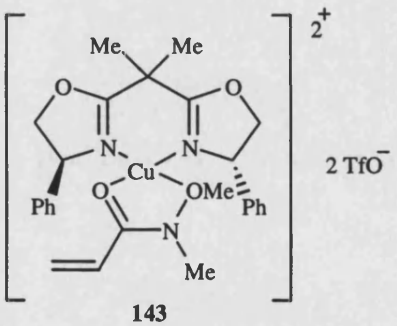
Table 19: effect of Lewis acid on the Diels-Alder reaction of acrylamide **138**

Lewis Acid (Temp.)	**Yield of 142**
$Yb(OTf)_3$ (RT)	56%
$Cu(OTf)_2$ (RT)	82%
$Cu(OTf)_2$ (-5 °C)	86%

The use of a Lewis acid does as expected increase the rate of cycloaddition for acrylamide **138**. In all cases, the Lewis acid itself is insoluble in DCM, however addition of the Weinreb acrylamide **138** causes the Lewis acid to become soluble, suggesting that it coordinates well to the acrylamide substrate. The reaction of $Yb(OTf)_3$ proceeds smoothly at room temperature however when $Cu(OTf)_2$ is utilised instead the reaction is more problematic. Initial formation of a blue solution, suggesting coordination of the $Cu(OTf)_2$ to the acrylamide functionality occurs, however when the reaction is left for a longer period (>5 h), the solution turns brown. Column chromatography allows isolation of the product as a brown oil, rather than the colourless oil obtained in the $Yb(OTf)_3$ reaction. This suggests that the stronger $Cu(OTf)_2$ catalyst also induces polymerisation of the acrylamide **138**. The quoted yield of this reaction is therefore inaccurate. These problems can be overcome by lowering the reaction temperature to –5 °C. At this temperature the reaction stays blue overnight and the desired cycloadduct can be isolated easily by column chromatography although the reaction is much slower requiring >30 h to proceed to completion. When the Diels-Alder adduct **142** is subjected to column chromatography two adducts can be isolated. ^{1}H NMR analysis suggests that the *endo* and *exo* adducts are separable. GC analysis of these samples is not straightforward. Instead of each sample allowing separation of the expected two isomers, four isomers can be separated. This can be attributed to the amide group being able to exist in either an *E* or *Z* conformation due to the resonance form where the nitrogen lone pair has donated to the carbonyl group.

Since a suitable Lewis acid has been found to carry out the catalysed Diels-Alder reaction of Weinreb acrylamide **138**, attention was turned to producing an asymmetric

version of this reaction. One of the most popular ligands used to obtain asymmetric variants of reactions utilising $Cu(OTf)_2$ as a catalyst are the bis(oxazolines), or BOX, ligands. The Diels-Alder reaction of many different *N*-acyl oxazolidinones has been carried out with high selectivity with a variety of dienes utilising $Cu(OTf)_2$-BOX asymmetric systems.[116] These reactions proceed *via* a six-membered transition state as has been shown to exist for the Et_2AlCl catalysed Diels-Alder reactions of *N*-acyl oxazolidinones first reported by Evans.[46] Reactions utilising BOX ligands can also proceed *via* a five-membered transition state. Glyoxylate-ene reactions,[117] and Mukaiyama aldol or hetero-Diels-Alder reactions using pyruvate esters,[118] have been shown to proceed *via* a five-membered transition state involving coordination between the copper metal centre and the two carbonyl groups of the pyruvate or glyoxylate substrates. This success led to the assumption that the Weinreb acrylamide **138** could coordinate to the copper metal centre in a five-membered transition state allowing enantioselectivity to be induced into the reaction by the BOX ligand (**Scheme 79**).



143

Scheme 79

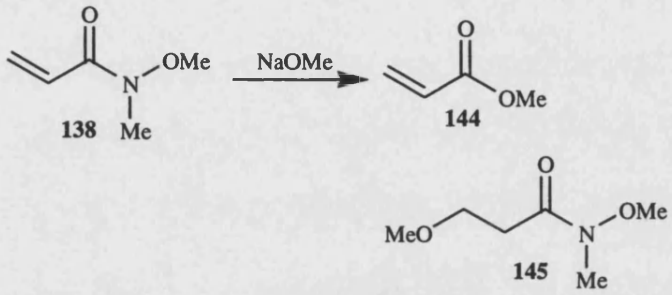
The reactions were carried out using both Weinreb acrylamide **138** and methyl vinyl ketone **140** as substrates. Unfortunately, no visible acceleration of the Diels-Alder reaction of Weinreb acrylamide **138** was noticed as is sometimes observed when ligands are utilised in Lewis acid catalysed reactions and the reaction was still incomplete after 20 h, whereas under identical conditions the reaction of methyl vinyl

ketone **140** was complete. ^{1}H NMR analysis showed that the reaction of ketone **140** proceeded in 14:1 *endo*:*exo* selectivity and that for Weinreb acrylamide **138** with 2:1 *endo*:*exo* selectivity. As the Diels-Alder reaction of Weinreb acrylamide **138** is considerably less selective than that for a simple ketone analogue, it appears as if, in this case, the proposed 5-membered transition state is disfavoured and as such no further attempts were made to improve upon this reaction.

The Diels-Alder reaction of the less reactive Weinreb cinnamide **139** was also examined. When the reaction was run using 10 mol% $Cu(OTf)_2$ as a catalyst an instant colour change to lime green was observed upon addition of cinnamide **139** to the suspension of Lewis acid. Although this changed to dark blue overnight, no problems were observed during chromatography suggesting no polymerisation had taken place in this case. However, according to ^{1}H NMR analysis, no cycloaddition occurred so a stronger Lewis acid was utilised. When either 1.1 Eq. or 1.5 Eq. Me_2AlCl was used as a catalyst, only starting material and cyclopentadiene dimer could be isolated suggesting no cycloaddition had occurred. It appears that this unreactive substrate requires considerable enhancement before cycloaddition can occur and the use of even a strong Lewis acid cannot overcome the highly electron–donating nature of the Weinreb amide functionality coupled with the presence of the phenyl group.

For even the acrylamide to be utilised as an activating, or possibly due to its highly unreactive nature a deactivating group, for the proposed catalytic chiral auxiliary cycle, a method for transesterification must be developed. Esters can be successfully converted into their Weinreb amide analogues by treatment with *N*-methoxy-*N*-methylamine hydrochloride and either an organomagnesium or aluminium based

reagent.[119] Attempts were made to determine if this reaction was reversible and as such Weinreb acrylamide **138** was treated with sodium methoxide and the crude reaction mixture examined for any traces of methyl acrylate **144**. However, by ^{1}H NMR analysis, no methyl acrylate was observed, rather conjugate addition product **145** was isolated by column chromatography. When the same reaction was carried out with the cinnamide substrate **139**, no reaction was observed at all suggesting this method of transesterification is inoperable.



Scheme 80

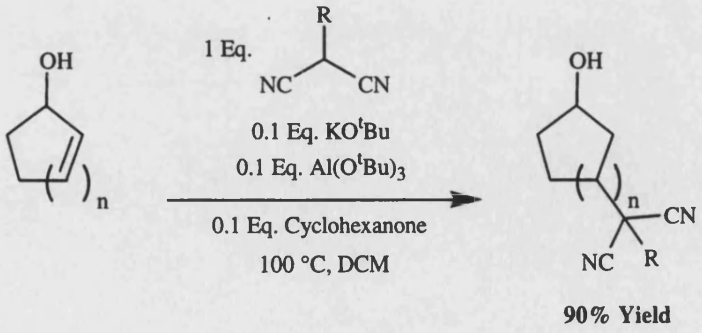
With these disappointing results, it was decided that the Weinreb amide functionality is not a suitable group for the proposed cycle and so further work was abandoned.

4.2 New "Impossible Reactions"

The proposed cycle whereby chiral auxiliaries can be used in a catalytic manner can be looked at in another way. Since the direct conversion between starting material and final product must be slow relative to the auxiliary catalysed pathway it can be said that activation by transformation into the auxiliary bound substrate allows an impossible reaction to be carried out. For instance, the "impossible" Diels-Alder reaction of carboxylate nucleophiles could be made to proceed by transformation into a suitable ester and, after reaction, removal of the ester group to reveal the desired carboxylate product. As such, *in situ* electronic activation of the starting material allows the reaction to proceed. There are many other impossible reactions that could

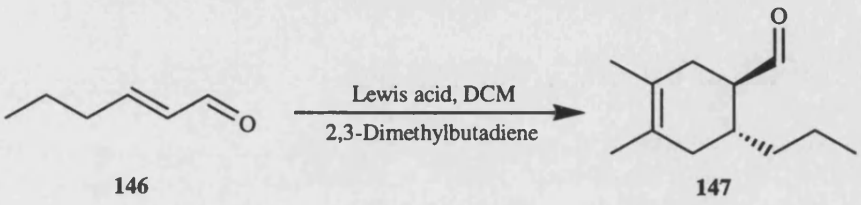
be made to proceed using this methodology, although it would be advantageous to examine those where the activation process is already known to be reversible.

Previous work within the group has examined the possibility of carrying out conjugate addition reactions on allylic alcohols.[120] This reaction is impossible, however oxidation of the allylic alcohol will generate the corresponding α,β-unsaturated ketone which is known to readily undergo conjugate addition reactions with a range of nucleophiles. Reduction of the conjugate addition product will then generate the desired alcohol addition product. In this case, the impossible reaction has been made to proceed *via in situ* electronic activation of the alcohol functionality. By utilising aluminium alkoxides catalysts alcohols can be oxidised to ketones in the Oppenauer oxidation reaction. The same catalysts can perform the analogous Meerwein-Ponndorf-Verley (MPV) reduction of ketones to alcohols.[121] By careful choice of conditions it should be possible to establish an equilibrium between alcohol and ketone and as such use this methodology as a way to activate allylic alcohols towards conjugate addition. Indeed this is possible and it has been shown that cyclic allylic alcohols can undergo conjugate addition via temporary activation as their ketone analogue.



Scheme 81

The ability to adapt this work to generate a procedure for the Diels-Alder reaction of allylic alcohols was examined. To simplify matters, primary alcohols were examined as no chiral centres are present and as such the ^{1}H NMR spectra of the cycloadducts should be relatively simple. For the same reason, the symmetrical 2,3-dimethylbutadiene was utilised as only one regioisomer is formed and as the product is not bicyclic, *endo* and *exo* regioisomers are unimportant. The first dienophile examined was *trans*-2-hexenal **146** and the ability of a range of Lewis acids to catalyse its Diels-Alder reaction. Aluminium-based Lewis acids would be useful as they can also be utilised in the MPV reduction and Oppenauer oxidation reactions.



146 **147**

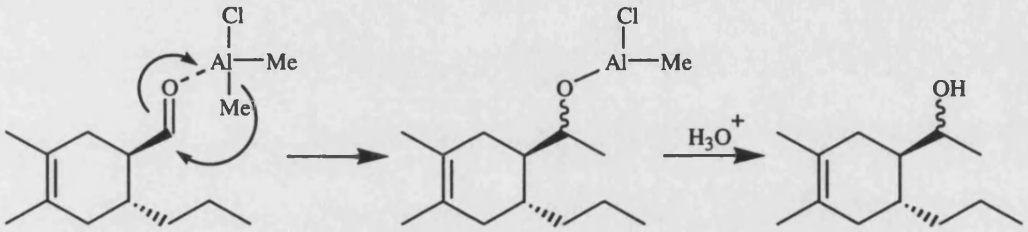
Scheme 82

Table 20: Effect of various Lewis acids on the Diels-Alder reaction of aldehyde **146**

Catalyst (Temp.)	Yield of 147
None (110 °C)	99%
10 mol% $AlMe_2Cl$ (RT)	60%
10 mol% $Al(O^iPr)_3$ (RT)	No Reaction
10 mol% $Al(O^iPr)_3$ (80 °C)	No Reaction
1 Eq. $Al(O^iPr)_3$ (RT)	No Reaction
1 Eq. $Al(O^tBu)_3$ (RT)	No Reaction
1.2 Eq. $Al(O^tBu)_3$ (70 °C)	No Reaction
20 mol% $Sc(OTf)_3$ (RT)	48%

The uncatalysed reaction of hexenal **146** proceeds smoothly when carried out in toluene at reflux in a sealed pressure tube to give the desired product in excellent isolated yield. It has recently been shown that $AlMe_2Cl$ can act as a catalyst for the MPV reduction of several carbonyl compounds by formation of low-aggregation aluminium alkoxides *in situ*.[122] It has also been shown to be a good Diels-Alder

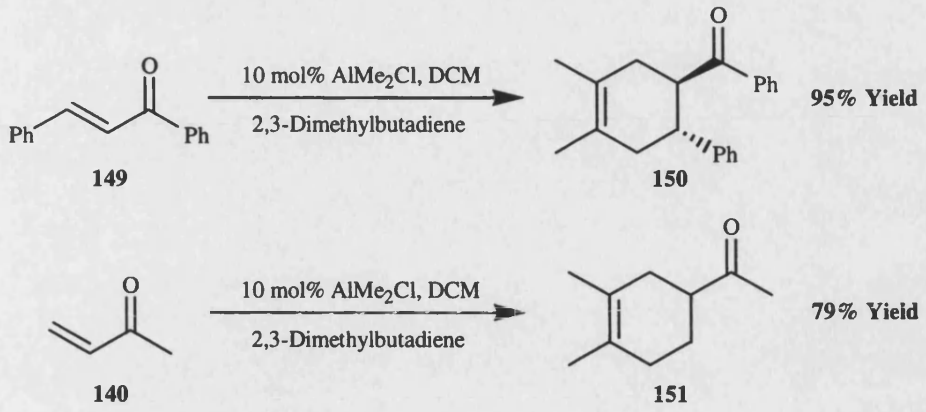
catalyst and the reaction of hexenal **146** proceeds in good yield, however an impurity can also be isolated, assigned the speculative structure **148** by NMR analysis. This is presumably formed by addition of a methyl group to the aldehyde in an analogous manner to the recently reported opening of epoxy sulfides by organoaluminiums,[123] and the chloroalkylation of aryl aldehydes by alkylboron dichlorides.[124] Aluminium alkoxide catalysts are the most commonly used for MPV reductions, however under a variety of conditions they were inactive as Diels-Alder catalysts. With the possible aim of using a mixed catalyst system, $Sc(OTf)_3$ was found to be a good cycloaddition catalyst.



147 **148**

Scheme 83

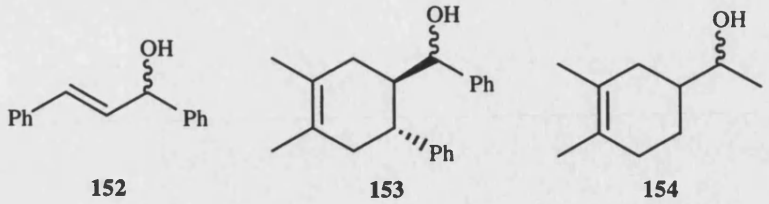
To avoid this undesired complication, the Diels-Alder reactions of methyl vinyl ketone **140** and chalcone **149** were investigated. The methyl transfer pathway should be retarded in these cases as the ketone functionality is less reactive towards nucleophilic attack and although a chiral centre will be formed in the final cycloadduct alcohol, a way to determine if any reaction has proceeded should be obtainable.



Scheme 84

Using just 10 mol% $AlMe_2Cl$ gives good conversion to both cycloadducts. However, when the reaction of chalcone **149** is run using 1.2 Eq. $Al(O^tBu)_3$ in DCM at reflux in a sealed pressure tube, no conversion to the desired cycloadduct **150** is observed.

Each of the corresponding alcohols which were not commercially available were reduced using either $NaBH_4$ for the cycloadducts **150** and **151** or $NaBH_4$ and $CeCl_3.7H_2O$ for the α,β-unsaturated chalcone **149**. All proceeded smoothly to give good yields of the desired products. The reduction of chalcone **149** to its alcohol **152** must be monitored carefully to minimise the production of any side-products that are formed under prolonged reaction conditions. Recrystallisation allows the adduct **152** to be isolated in 75% yield. The production of reduced chalcone cycloadduct **153** also proceeds smoothly. After column chromatography adduct **153** can be isolated as a viscous colourless oil in 86% yield. The methyl vinyl ketone cycloadduct **151** can also be reduced to the corresponding alcohol **154** to give the desired cycloadduct in 86% yield after column chromatography.

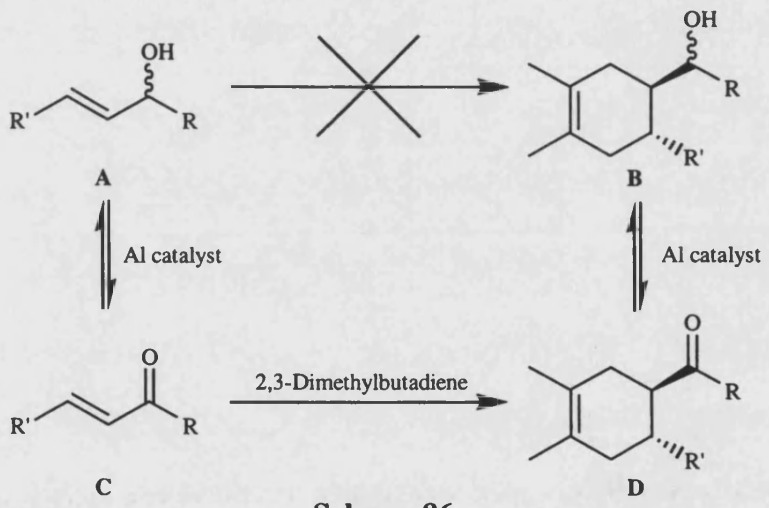


152 153 154

Scheme 85

With all these products available, the possibility of using them as adducts in the tandem MPV reduction and Oppenauer oxidation reaction was examined.

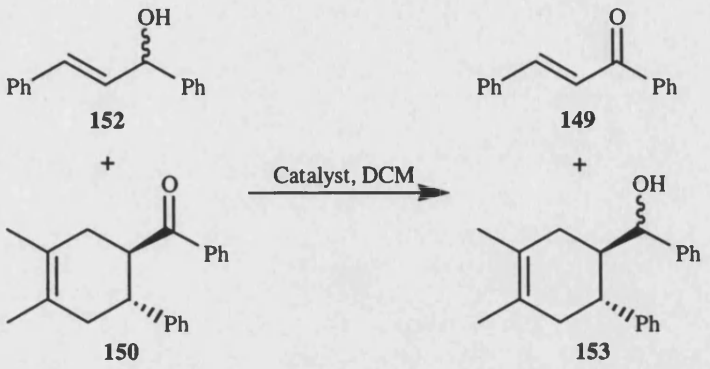
4.3 Tandem MPV reductions and Oppenauer oxidations



Scheme 86

The proposed cycle is shown in **Scheme 86** and the direct transformation between alcohol **A** and **B** is known to be impossible. As has been shown Diels-Alder reaction of aldehyde or ketone **C** to form cycloadduct **D** proceeds well in the presence of a suitable catalyst. It remains to see if the tandem MPV reduction and Oppenauer oxidation can be made to occur for these substrates. The easiest way to do this would be take mixtures of **A** and **D** or **B** and **C** with a catalyst and see if the reaction occurs to produce **B** and **C** or **A** and **D** respectively. All reactions were run in an analogous manner with the aluminium catalyst being added slowly to a stirred solution of the

alcohol. After allowing fifteen to thirty minutes for formation of the alkoxide to occur a solution of the requisite ketone was added and the reaction left at the desired temperature overnight.

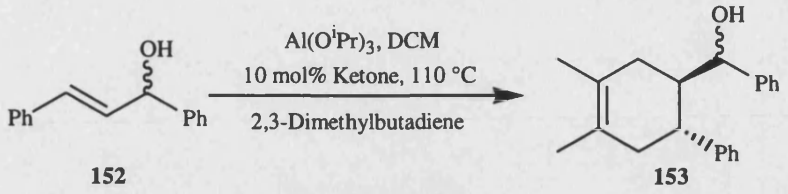


Scheme 87

When a 1:1 mixture of reduced chalcone **152** and Diels-Alder adduct **150** were mixed in the presence of 1.2 Eq. $AlMe_2Cl$, ^1H NMR analysis shows no chalcone **149** or reduced chalcone **152** to be present. The Diels-Alder adducts **150** and **153** are present in a ratio of 1:1. The reverse reaction where chalcone **149** is mixed with reduced Diels-Alder adduct **153** and 1.2 eq. $AlMe_2Cl$ shows only chalcone **149** by ^1H NMR analysis. It appears as if the strong Lewis acid is having an adverse effect on the reaction and therefore, the less reactive aluminium alkoxides were examined. When the tandem MPV reduction and Oppenauer oxidation between chalcone **149** and reduced cycloadduct **153** is attempted using 1.2 Eq. $Al(O^iPr)_3$ at room temperature, no reaction is observed as determined by ^1H NMR analysis which shows just a 1:1 mixture of the starting materials. When the reaction between reduced chalcone **152** and Diels-Alder adduct **150** is run in DCM at reflux with 1.2 Eq. $Al(O^iPr)_3$, mainly starting material is seen by ^1H NMR analysis, however some very small peaks which relate to chalcone **149** and reduced cycloadduct **153** are observed. Conversion, as estimated by relative integral heights is less than 5%. Changing to $Al(O^tBu)_3$ shows some conversion has also occurred, although in this case the peaks for the reduced

cycloadduct **153** are very small, making the best estimate at conversion to be less than 2%. To see if this conversion could be increased, the reaction was re-run in DCM at reflux in a sealed pressure tube (oil bath temperature = 110 °C). ^{1}H NMR analysis of the reaction using 1.2 Eq. $Al(O^tBu)_3$ showed no peaks corresponding to either of the reduced adducts, however the reaction using 1.2 Eq. $Al(O^iPr)_3$ showed a 1:2:2:1 mixture of adducts **149**:**152**:**153**:**150** respectively. Peaks corresponding to an impurity were also observed on a comparable scale to the desired products. This was speculatively assigned to be a dimeric chalcone species, although no other data was obtained to support a definite strucure.

Since some tandem MPV reduction and Oppenauer oxidation can be obtained using 1.2 Eq. $Al(O^iPr)_3$ under forcing conditions, attempts were made to obtain a working catalytic cycle starting from reduced chalcone **152** and using 10 mol% of an added ketone as a hydride acceptor.



152 **153**

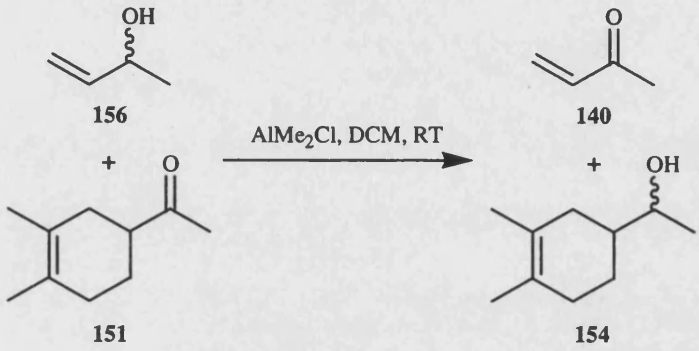
Scheme 88

Table 21: Tandem MPV/Oppenauer/cycloaddition of reduced chalcone **152**

Catalyst	Ketone	Concentration	^{1}H NMR analysis
1.2 Eq.	None	0.5 M	**152**, impurity and a little **149**.
1.2 Eq.	**150**	0.5 M	Mix of **152**, **150**, **149** but mainly impurity.
1.2 Eq.	**150**	0.25 M	Mix of **152**, **150**, **149** but mainly impurity.
0.1 Eq.	**150**	0.5 M	**149**:**152**:**150**:**153**= 1:4:2:0 and lots of impurity.
1.2 Eq.	None	0.5 M	Mix of **149** and **152** but mainly impurity.
1.2 Eq.	**149**	0.25 M	Mix of 149, 152 and impurity. Very little Diels-Alder adducts.
0.1 Eq.	**149**	0.5M	**149**:**152**:**150**:**153**= 2:5:2:0 and lots of impurity,
1.2 Eq. + 10 mol% Yb(OTf)$_3$	**149**	0.5 M	Impurity
0.1 Eq. + 10 mol% Yb(OTf)$_3$	**149**	0.5 M	Impurity

When either ketone source was absent from the reaction mixture the main product of the reaction was the impurity. Reduced chalcone **152** and chalcone **149** could also be observed, suggesting that decompostion of starting material may be a major problem. In all cases when added ketone was used, none of the desired final cycloadduct **153** was observed and the production of the impurity was the major reaction. The addition of Yb(OTf)$_3$ as a co-catalyst only exasperated this effect so mush so that none of the intermediates in the proposed cycle were observed by ^{1}H NMR analysis. It appears as if the use of chalcone derivatives in the proposed full cycle is problematic and so the use of other adducts was examined.

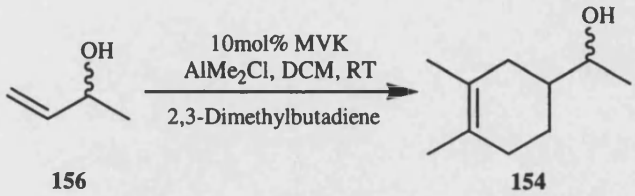
Trans-2-hexen-1-al **146** also proved to be a difficult substrate to use. The use of $AlMe_2Cl$ as a tandem MPV reduction and Oppenauer oxidation catalyst would be undesirable since the resultant cycloadducts may be subject to methyl transfer. However, since aluminium alkoxides do not promote the Diels-Alder reaction, their use as tandem MPV reduction and Oppenauer oxidation catalysts will also be limited. As an alternative, the use of methyl vinyl ketone **140** and buten-2-ol **156** as suitable substrates was examined.



Scheme 89

The ability to carry out a tandem MPV reduction and Oppenauer oxidation was examined using $AlMe_2Cl$ as a catalyst. In all cases examined, the volatility of methyl vinyl ketone **140** and its alcohol analogue **156** may prejudice any conversion obtained, therefore these substrates were removed *in vacuo* and conversions determined by analysis of the crude ^1H NMR of the cycloadducts obtained. When 10 mol % of catalyst is used, the tandem oxidation/reduction occurs between allyl alcohol **156** and cycloadduct **151** to give 20% conversion into Diels-Alder alcohol **154**. The reverse reaction starting with Diels-Alder alcohol **154** shows conversion into the corresponding ketone **151** also in 20% as determined by ^1H NMR analysis. When 1.2 Eq. $AlMe_2Cl$ is used as the catalyst the reaction proceeds less smoothly. Starting from Diels-Alder ketone **151**, the reaction proceeds with less than 10% conversion whereas starting from the corresponding alcohol ^1H NMR analysis shows that the ketone **151** is

barely detectable, suggesting very low conversion. This may be caused by the vigorous evolution of a gas, presumably HCl, when methyl vinyl ketone **140** is added to the alcohol/Me_2AlCl mixture. This may cause the loss of some of the methyl vinyl ketone, giving a poor result. Even when the addition is carried out at –78 °C the evolution occurs which could cause problems with the use of this system in the tandem MPV/Oppenauer/cycloaddition cycle, however such a cycle was attempted.



156 **154**

Scheme 90

Table 22: Tandem MPV/Oppenauer/cycloaddition of allylic alcohol **156**

Catlayst	Ketone	^{1}H NMR analysis
0.1 Eq. $AlMe_2Cl$	None	Mainly **156**
0.1 Eq. $AlMe_2Cl$	10 mol% MVK	**156**:**154**:**151**= 66:≈7:27
1.2 Eq. $AlMe_2Cl$	10 mol% MVK	**156**:**154**:**151**= 77:0:23

Each reaction was run as before although careful removal of solvents *in vacuo* allowed a majority of the starting alcohol **156** to be retained, although methyl vinyl ketone **140** is too volatile to be isolated. Analysis of the crude ^{1}H NMR spectra allows determination of the ratios of products. When no ketone is added to the reaction, as expected mainly starting material is observed. By using 10 mol% $AlMe_2Cl$ and 10 mol% methyl vinyl ketone **140**, all adducts expected can be observed. Again the starting material is the main adduct present although the ketone Diels-Alder adduct **151** is present in a substantial amount. In addition a small amount of the desired Diels-Alder alcohol **154** can be seen. Since there is more then 10% of the ketone product and some of the desired overall product is observed, it appears as if the proposed cycle is valid, however conditions must be engineered to improve the overall yield. By using 1.2 Eq. $AlMe_2Cl$, the ketone cycloadduct **151** can again be observed, although

in this case, no Diels-Alder alcohol **154** is seen by ^{1}H NMR analysis. This is not altogether surprising as the tandem MPV/Oppenauer reaction proceeds less smoothly with 1.2 Eq. $AlMe_2Cl$ and therefore the overall transformation will be slower than when catalytic amounts are used.

In conclusion, the ability to carry out the "impossible" Diels-Alder reaction of allylic alcohols appears to be attainable. Further engineering of the cycle should result in a substrate/catalyst system that is amenable to both the cycloaddition and tandem MPV reduction and Oppenauer oxidation.

Chapter 5

Experimental

5) Experimental

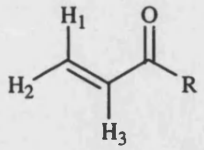
5.1 General Experimental

Commercially available reagents and solvents were used throughout without further purification, except for those described below which were purified as described. Reactions were commonly run in HPLC grade solvent, whereas during work-up and purification standard grade solvents were used. When a solvent is described as being dry, the standard grade solvent was distilled from an appropriate drying agent. DCM and MeCN were dried with KOH and freshly distilled from CaH_2 under nitrogen prior to use. THF and diethyl ether were distilled from sodium benzophenone ketyl, and toluene and hexane were distilled from sodium under nitrogen prior to use. Triethylamine was dried by distillation from CaH_2 and stored over 4Å molecular sieves. Cyclopentadiene was freshly prepared from dicyclopentadiene by distillation through a Vigreaux column.

Analytical thin layer chromatography was carried out using plastic backed plates coated with Merck Kieselgel 60 GF_{240}. Plates were visualised using UV light (254nm) and/or by staining with potassium permanganate followed by heating. Flash chromatography was carried out on Merck Kieselgel 60 H silica according to the procedure of Still *et al.*[126] Samples were applied pre-absorbed on silica or as saturated solutions in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600cm^{-1} using a Perkin Elmer 1605 FT-IR spectrometer and were recorded either neat or as nujol mulls. Elemental analysis was carried out on a Carbo-Erba Stametazione EA 1506 analyser. Melting points were measured on a Gallenkamp single stage apparatus and are uncorrected. Mass spectroscopy was carried out by the University of Bath Mass Spectroscopy

service. ^{1}H and ^{13}C NMR spectra were recorded using Jeol GX 270, Bruker GX 300 and Bruker GX 400 instruments at the frequency indicated and are referenced to TMS. Gas chromatography was determined on a Fisions series 8000 GC using a chiral β-dex 120, 60M x 0.25mm. 0.25ID column and the conditions outlined in the relevant experiment.



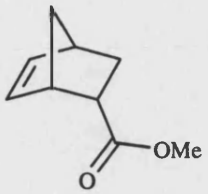
Nomenclature for alkenes

5.2 Experimental for Chapter 2

General procedure (1) for preparation of authentic Diels-Alder adducts

Oxalyl chloride (0.40 mL, 4.6 mmol, 1 Eq.) was added dropwise to a stirred solution of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (0.636 g, 4.6 mmol, 1 Eq.) and dry dimethylformamide (25 μL) in dry DCM (6 mL) under nitrogen at 0 °C. After 5 min (gas liberation ceased) the mixture was heated to 32 °C until gas liberation again ceased. Once cooled the resultant acid chloride was transferred *via* syringe to a stirred solution of alcohol (6.9 mmol, 1.5 Eq.), anhydrous triethylamine (0.96 mL, 6.9 mmol, 1.5 Eq.) and catalytic DMAP in anhydrous DCM (6 mL) at 0 °C under nitrogen. The reaction was allowed to warm to room temperature and stirred for 18 hours and then partitioned between diethyl ether (100 mL) and saturated aqueous potassium bicarbonate (100 mL). The aqueous phase was extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The resultant oil was purified by column chromatography to afford the desired esters.

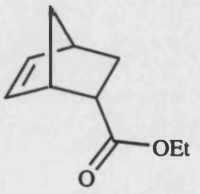
Methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate 85



$C_9H_{12}O_2$
Mol. Wt.: 152.19

Title compound was obtained as a colourless oil. (0.61 g, 4.0 mmol, 87% yield); ν_{max} (film)/cm^{-1} 3061, 2975, 2874, 1736, 1437, 1336, 1270, 1197, 1110, 1065, 1033, 901, 835, 774, 713; GC (β-dex column, 110 °C) t_r = 28.0 min, 28.2 min (*exo*), 33.9 min, 34.7 min (*endo*); ^{1}H NMR identical to that reported.[127]

Ethyl bicyclo[2.2.1]hept-5-ene-2-carboxylate 87

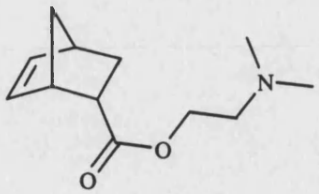


$C_{10}H_{14}O_2$
Mol. Wt.: 166.22

Title compound was isolated as a colourless oil. (0.69 g, 4.1 mmol, 90% yield); GC (β-dex column, 110 °C) t_r = 36.2 min, 36.9 min (*exo*), 44.0 min, 45.4 min (*endo*); ν_{max} (film)/cm^{-1} 3062, 2997, 2874, 1732 (C=O), 1450, 1370, 1335, 1270, 1185, 1106, 1040, 712; δ_H (270 MHz; $CDCl_3$) 1.23 (3H, t, *J* 7.2, OCH_2CH_3 *endo*), 1.27 (3H, t, *J* 7.2, OCH_2CH_3 *exo*), 1.20-1.95 (4H, m, CH & CH_2), 2.22-2.97 (2H, m, CH), 3.04 (1H, brd s, $CHCO_2$ *exo*), 3.21 (1H, brd s, $CHCO_2$ *endo*), 4.04-4.19 (2H, m, OCH_2CH_3), 5.92-6.21 (2H, m, HC=C).

Identical to literature data.[70b]

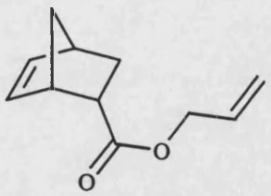
2-(Dimethylamino) ethyl bicyclo[2.2.1]hept-5-ene-2-carboxylate 90



$C_{12}H_{19}NO_2$
Mol. Wt.: 209.28

Title compound was isolated as a colourless oil (0.73 g, 3.5 mmol, 75% yield); R_f (10% EtOAc/ light petroleum) 0.38; GC (β-dex column, 170 °C) t_r = 14.3 min (*exo*), 16.4 min, 17.0 min (*endo*); ν_{max} (film)/cm^{-1} 3061, 2973, 2770, 1733, 1457, 1335, 1271, 1174, 1111, 1064, 1032, 906, 838, 711; δ_H (270 MHz; $CDCl_3$) 1.30-1.37 (2H, m, CH & CH_2), 1.83 (1H, ddd, *J* 3.7, 9.0, 12.2, *CH),* 2.21 (6H, s, $N(CH_3)_2$), 2.47 (2H, t, *J* 5.9, NCH_2), 2.82 (1H, brd s, C=C-C*H*-C-C=O), 2.91 (1H, dt, *J* 9.3, 4.0, CH-C=O), 3.14 (1H, brd s, CH-C=C), 4.05 (2H, t, *J* 5.7, O-CH_2), 5.86 (1H, dd, *J* 5.7, 2.8, =CH), 6.12 (1H, dd, *J* 5.7, 2.9, =CH); δ_c (67.9 MHz; $CDCl_3$) 29.0, 30.2, 41.5, 42.2, 43.0, 43.3, 45.6 (N-CH_3), 46.5, 45.9, 49.4, 46.7, 57.7 (CH_2-N), 62.0 (CH_2-O), 135.8, 132.1, 138.0, 137.6, 176.1, 174.5 (C=O).

Allyl bicyclo[2.2.1]hept-5-ene-2-carboxylate 103



$C_{11}H_{14}O_2$
Mol. Wt.: 178.23

The title compound was isolated as a colourless oil (0.43 g, 2.4 mmol, 52% yield); R_f (15% Et_2O/ light petroleum) 0.44, 0.51; ν_{max} (film)/cm^{-1} 3058, 2982, 2872, 1722, 1647, 1446, 1335, 1270, 1182, 1109, 1029, 932, 756, 711; δ_H (400 MHz; $CDCl_3$) 1.28

(1H, d, *J* 4.7, CH *endo*), 1.34-1.46 (2H, m, CH_2), 1.54 (1H, d, *J* 4.7, CH *exo*), 1.88-1.96 (1H, m, CH), 2.24-2.28 (1H, m, CH *exo*), 2.91 (1H, brd s, CH), 2.96-2.99 (1H, m, CH *endo*), 4.50-4.58 (2H, m, O-CH_2 *endo*), 4.58-4.79 (2H, m, O-CH_2 *exo*), 5.18-5.26 (1H, m, =CH), 5.28-5.35 (1H, m, =CH), 5.85-5.99 (2H, m, =CH), 6.10-6.20 (1H, m, =CH); δ_c (100.6 MHz, $CDCl_3$) 29.3, 30.4, 34.7, 41.2, 41.7, 42.5, 43.1, 43.1, 45.2, 45.7, 46.1, 46.4, 49.6, 50.3, 54.8, 64.8 (O-CH_2), 65.1 (O-CH_2), 117.8, 118.0, 132.0, 132.3, 132.4, 132.5, 135.7, 136.0, 137.7, 138.1, 174.3 (C=O), 175.8 (C=O); *m/z* (EI) 178.1 (M^+, 25%), 137.0 (38%), 66.0 (100%); (Found: M^+ 178.0977. $C_{11}H_{14}O_2$ requires 178.0994).

Identical to literature data.[29]

General procedure (2) for Diels-Alder reactions of acrylates

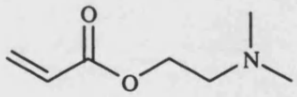
Freshly prepared cyclopentadiene monomer (5 Eq.) was added to a stirred solution of the desired acrylate (1 Eq.) in dry solvent (0.25 M solution) at room temperature under nitrogen. The reaction mixture was stirred at room temperature until no more starting material was observed by TLC analysis. The solvent and excess diene were removed *in vacuo* and the resultant oil purified *via* column chromatography (10% EtOAc/ light petroleum) to yield the desired Diels-Alder adducts.

General procedure (3) for competition Diels-Alder reactions between acrylic acid 82 and ethyl acrylate 86

Freshly prepared cyclopentadiene monomer (0.57 mL, 6.95 mmol, 5 Eq.) was added to a stirred solution of acrylic acid **82** (0.10 g, 1.39 mmol, 1 Eq.), ethyl acrylate **86** (0.15 mL, 1.39 mmol, 1 Eq.) and additive, if used, in dry solvent (4 mL) at room temperature under nitrogen. After 7 h the reaction mixture was partitioned between

diethyl ether (20 mL) and saturated brine and hydrochloric acid (20 mL, pH <2). The aqueous phase was extracted with diethyl ether and the combined organic phases dried over $MgSO_4$ and evaporated to dryness. The resultant oil was dissolved in diethyl ether (10 mL) and at room temperature nitrogen/diazomethane (prepared *in situ* by bubbling nitrogen through a solution of Diazald® (1.0 g) in ethanol (15 mL) and excess potassium hydroxide pellets, yellow solution) was bubbled through *via* cannula. After complete reaction of the Diazald® (formation of white suspension) the solvent was evaporated and the crude mixture purified by column chromatography (10% Et_2O/ light petroleum) to afford a mixture of methyl and ethyl esters as a colourless oil. The ratios were determined by GC analysis.

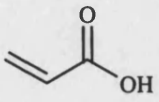
Analysis of 2-(dimethylamino)ethyl acrylate 88



$C_7H_{13}NO_2$
Mol. Wt.: 143.18

Analysis of this commercially available product was carried out to enable determination of the rate of cycloaddition. GC (β-dex column, 170 °C) t_r = 5.1 min; δ_H (270 MHz; $CDCl_3$) 2.32 (6H, s, $N(CH_3)_2$), 2.54 (2H, t, *J* 5.6, N-CH_2), 4.19 (2H, t, *J* 5.6, O-CH_2), 5.76 (1H, dd, *J* 10.3, 1.6, H_2), 6.09 (1H, dd, *J* 17.3, 10.3, H_3), 6.35 (1H, dd, *J* 17.3, 1.6, H_1).

Analysis of acrylic acid 82



$C_3H_4O_2$
Mol. Wt.: 72.06

Obtained commercially but for comparison: GC (β-dex column, 170 °C) t_r = 4.4 min.

Calibration of GC for competition reactions

Prior to competition reactions, standard samples of known composition were analysed by GC. By comparison of the observed ratio of starting material to product to the known ratio of each sample a calibration curve could be plotted. This was used to determine the actual composition of any samples analysed. The derived equations for the calibration curves are:

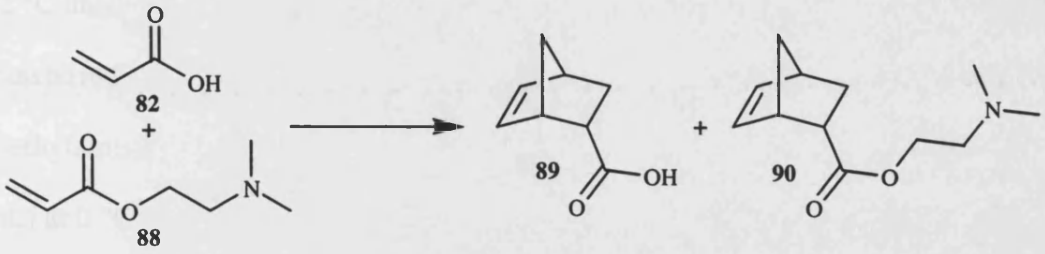
Acrylic Acid **82**: Real % = -0.0086(Obs %)^2 + 1.8601(Obs %).

Bicyclo [2.2.1] hept-5-ene-2-carboxylic acid **83**: Real % = 0.0083(Obs %)^2 + 0.1605(Obs %).

2-(Dimethylamino) ethyl acrylate **88**: Real % = -0.0067(Obs %)^2 + 1.6597(Obs %).

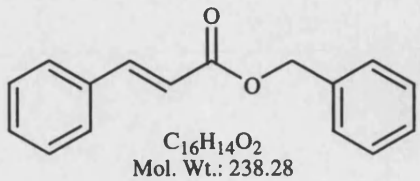
2-(Dimethylamino) ethyl bicyclo [2.2.1] hept-5-ene-2-carboxylate **90**: Real % = 0.0059(Obs %)^2 + 0.3844(Obs %).

General procedure (4) for competition Diels-Alder reactions between acrylic acid 82 and 2-(dimethylamino)ethyl acrylate 88



Freshly prepared cyclopentadiene monomer (4.12 mL, 0.05 mol, 5 Eq.) was added to a stirred solution of acrylic acid **82** (0.68 mL, 0.01 mol, 1 Eq.) and 2-(dimethylamino) ethyl acrylate **88** (1.52 mL, 0.01 mol, 1 Eq.) in DCM (20 mL) at room temperature under nitrogen. Aliquots were taken every 30 minutes and conversion determined by GC analysis after prior calibration with known standards.

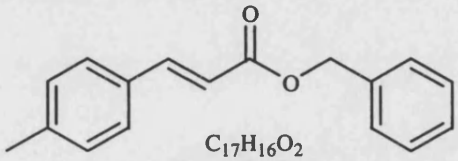
Analysis of benzyl (2*E*)-3-phenyl-2-propenoate 91



$C_{16}H_{14}O_2$
Mol. Wt.: 238.28

Obtained commercially but for comparison: δ_H (270 MHz; $CDCl_3$) 5.25 (2H, s, CH_2), 6.48 (1H, d, *J* 16.1, O=C-HC=), 7.32-7.43 (8H, m, Ar-H), 7.48-7.52 (2H, m, Ar-H), 7.73 (1H, d, *J* 16.1, Ar-HC=).

Synthesis of benzyl (2*E*)-3-*p*-tolyl-2-propenoate 92



$C_{17}H_{16}O_2$
Mol. Wt.: 252.31

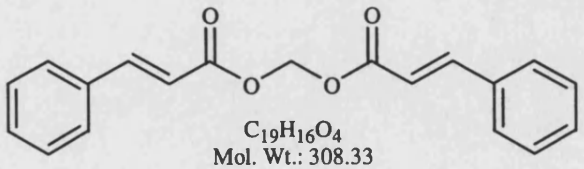
Oxalyl chloride (0.35 mL, 4 mmol, 1 Eq.) was added dropwise to a stirred solution of 4-methyl cinnamic acid (0.65 g, 4 mmol, 1 Eq.) and dry DMF (25μL) in dry DCM (10 mL) at 0 °C under nitrogen. After gas liberation had ceased, the solution was heated to 32 °C until gas liberation again ceased. Once cooled, the resultant acid chloride was transferred *via* syringe to a solution of benzyl alcohol (0.41 mL, 4 mmol, 1 Eq.), triethylamine (1.1 mL, 8 mmol, 2 Eq.) and catalytic DMAP (10 mg) in dry DCM (6 mL) at 0 °C under nitrogen. The reaction was stirred at this temperature for 20 min and then warmed to room temperature for 7 hours. The reaction was quenched with 2M HCl (10 mL) and extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography (40% EtOAc/ light petroleum) to afford the desired ester as a colourless solid (0.92 g, 3.64 mmol, 91%); R_f 0.33 (15% Et_2O/ light petroleum); υ_{max} (nujol)/cm^{-1} 2866, 2919, 1709, 1638, 1454, 1379, 1312, 1213, 1162, 1008, 985, 903,

814, 697; δ_H (270 MHz; $CDCl_3$) 2.36 (3H, s, Ar-CH_3), 5.24 (2H, s, CH_2), 6.44 (1H, d, *J* 15.9, O=C-HC=), 7.18 (2H, d, *J* 8.1, Ar-H), 7.31-7.43 (7H, m, Ar-H), 7.71 (1H, d, *J* 15.9, Ar-HC=); δ_c (75.5 MHz; $CDCl_3$) 21.5 (Ar-CH_3), 66.3 (O-CH_2), 116.7 (=CH-C=O), 128.1, 128.2, 128.3, 128.6, 129.6, 131.6, 136.1, 140.8, 145.2 (Ar-CH=), 167.0 (C=O); *m/z* (EI) 252.1 (M^+, 22%), 207.1 (22%), 145.0 (37%), 91.0 (100%); (Found: M^+ 252.1141. $C_{17}H_{16}O_2$ requires 252.1150) (Found: C, 80.5, H, 6.65. $C_{17}H_{16}O_2$ requires C, 80.9, H, 6.39).

General procedure (5) for the attempted reversible benzyl transfer reaction

A solution of 4-methyl benzyl (2*E*)-3-*p*-tolyl-2-propenoate **92** (0.126 g, 0.5 mmol, 1 Eq.) in an appropriate solvent (20 mL) was added to a salt of cinnamic acid (1 Eq., deprotonated with a suitable base prior to reaction). This was left at the desired temperature overnight when the reaction was quenched with 2M NaOH. The aqueous layer was extracted with DCM, dried over $MgSO_4$ and evaporated to dryness. Any esters **91** and **92** produced were isolated as a colourless solid by column chromatography (15% Et_2O/ light petroleum). Analysis of the ^1H NMR of the isolated substance determined that no transesterification had occurred.

Synthesis of methylidene dicinnamate 93



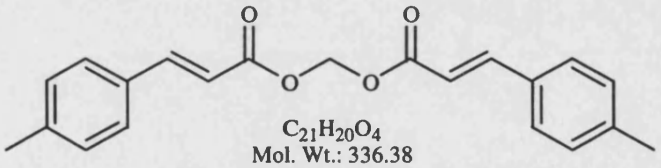
$C_{19}H_{16}O_4$
Mol. Wt.: 308.33

Synthesised according to general procedure **5** using tetrabutyl ammonium cinnamate as the nucleophile and DCM as the solvent. The title product was separated form the corresponding 4-methyl benzyl (2*E*)-3-*p*-tolyl-2-propenoate **92** by column

chromatography (15% Et_2O/ light petroleum) and obtained as a colourless solid (290 mg, 0.095 mmol, 38%); R_f (15% Et_2O/ light petroleum) 0.21; υ_{max} (nujol)/cm^{-1} 2956.3, 2937.2, 2856.2, 1731.6, 1641.1, 1450.5, 1317.1, 1169.3, 1116.9, 993.0, 969.0, 869.1, 769.1, 716.6, 669.0; δ_H (300 MHz; $CDCl_3$) 6.04 (2H, s, OCH_2O), 6.49 (2H, d, *J* 16.0, =CH), 7.36-7.44 (6H, m, Ar-H), 7.51-7.58 (4H, m, Ar-H), 7.81 (2H, d, *J* 16.0, =CH); δ_c (75.5 MHz; $CDCl_3$) 78.4 (OCH_2O), 115.8 (CH), 127.4 (CH), 128.0 (CH), 129.8 (CH), 133.1 (Ar-C), 145.9 (CH), 164.6 (C=O).

Identical to literature data.[75]

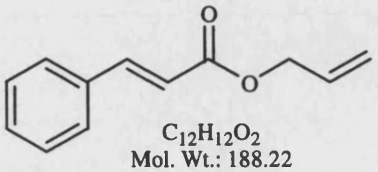
Synthesis of methylidene di-(4-methyl)cinnamate 94



$C_{21}H_{20}O_4$
Mol. Wt.: 336.38

The title compound was synthesised in a similar manner as methylidene dicinnamate **93** although tetrabutyl ammonium (4-methyl)cinnamate was used as a nucleophile (336 mg, 0.1 mmol, 40%) R_f (15% Et_2O/ light petroleum) 0.21; Mp 117-119 °C; δ_H (270 MHz; $CDCl_3$) 2.37 (6H, s, CH_3), 6.02 (2H, s, OCH_2O), 6.42 (2H, *J* 15.8, =CH), 7.12 (4H, d, *J* 8.3, Ar-H), 7.42 (4H, d, *J* 8.3, Ar-H), 7.76 (2H, d, *J* 15.8, =CH); δ_c (100.6 MHz; $CDCl_3$); 21.9 (CH_3), 79.6 (OCH_2O), 115.9 (CH), 128.5 (CH), 129.9 (C), 131.5 (C), 141.1 (C), 146.9 (CH), 165.9 (C=O); *m/z* (FAB^+) 337.1 (MH^+, 82%), 173.1 (21%), 145.1 ($C_{10}H_9O$, 100%).

Synthesis of allyl (2*E*)-3-phenyl-2-propenoate 98



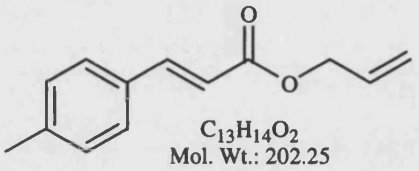
$C_{12}H_{12}O_2$
Mol. Wt.: 188.22

Oxalyl chloride (2.62 mL, 30 mmol, 1 Eq.) was added dropwise to a stirred solution of cinnamic acid (4.45 g, 30 mmol, 1 Eq.) and dry dimethylformamide (25 μL) in anhydrous diethyl ether (10 mL) under nitrogen at 0 °C. After 5 min (gas liberation ceased) the mixture was heated to 32 °C until gas liberation again ceased. Once cooled the resultant acid chloride was transferred dropwise *via* syringe to a stirred solution of allyl alcohol (3.06 mL, 45 mmol, 1.5 Eq.), anhydrous triethylamine (4.87 mL, 35 mmol, 1.2 Eq.) and catalytic DMAP in anhydrous diethyl ether (30 mL) at 0 °C under nitrogen. The reaction was stirred at this temperature for 20 min and then warmed to room temperature for 7 hours. The reaction was quenched with 2M HCl (10 mL) and extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography (15% Et_2O/ light petroleum) to afford the desired ester as a colourless oil (3.7g, 19 mmol, 63%); R_f (15% Et_2O/ light petroleum) 0.29; υ_{max} (film)/cm^{-1} 3055, 3026, 2941, 1709, 1637, 1577, 1495, 1449, 1358, 1310, 1254, 1160, 984, 932, 864, 767, 694; δ_H (270 MHz; $CDCl_3$) 4.71 (2H, dt, *J* 5.7, 1.4, O-CH_2), 5.27 (1H, dd, *J* 10.4, 1.4, H_2), 5.37 (1H, dd, *J* 17.2, 1.4, H_1), 6.00 (1H, ddt, *J* 17.2, 10.4, 5.7, H_3), 6.47 (1H, d, *J* 16.1, O=C-CH), 7.37-7.39 (3H, m, Ar-H), 7.51-7.55 (2H, m, Ar-H), 7.72 (1H, d, *J* 16.1, Ar-HC=); δ_c (75.5 MHz; $CDCl_3$) 65.1 (O-CH_2), 117.8 (=*C*H-C=O), 118.2 (=CH_2), 128.1, 128.6, 130.0, 130.3, 132.3, 134.3, 145.0 (Ph-CH=), 166.5 (C=O); *m/z* (EI) 188.1 (M^+,

9%), 143.1 (11%), 131.0 (68%), 103.0 (30%), 77.0 (21%), 66.0 (13%), 51.0 (8%), 28.0 (100%); (Found: M^+ 188.0828. $C_{12}H_{12}O_2$ requires 188.0837).

Identical to literature data.[128]

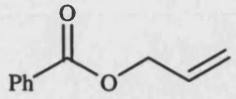
Synthesis of allyl (2*E*)-3-*p*-tolyl-2-propenoate 100



$C_{13}H_{14}O_2$
Mol. Wt.: 202.25

The title product was synthesised in a similar manner to allyl (2*E*)-3-phenyl-2-propenoate **98** and was obtained as a colourless oil (5.2 g, 26 mmol, 85% yield); R_f (15% Et_2O/ light petroleum) 0.29; υ_{max} (film)/cm^{-1} 3084, 3026, 2931, 1712, 1697, 1536, 1513, 1309, 1283, 1193, 1166, 1017, 983, 932, 812; δ_H (270 MHz; $CDCl_3$) 2.38 (3H, s, Ar-CH_3), 4.71 (2H, dt, *J* 5.9, 1.5, O-CH_2), 5.25-5.46 (2H, m, =CH_2), 5.90-6.07 (1H, m, H_3), 6.42 (1H, d, *J* 16.1, O=C-HC=), 7.18-7.26 (2H, m, Ar-H), 7.41-7.49 (2H, m, Ar-H), 7.69 (1H, d, *J* 16.1, Ar-HC=); δ_c (75.5 MHz; $CDCl_3$) 21.5 (Ar-CH_3), 65.1 (O-CH_2), 116.7 (=CH-C=O), 118.2 (=CH_2), 128.1, 129.6, 131.6, 132.4, 140.7, 145.1 (Ph-CH=), 166.8 (C=O); *m/z* (EI) 202.1 (M^+, 23%), 157.1 (19%), 145.0 (100%), 131.0 (12%), 118.1 (64%), 91.0 (23%), 43.0 (75%), 28.0 (39%); (Found: M^+ 202.0992. $C_{13}H_{14}O_2$ requires 202.0994).

Synthesis of allyl benzoate 99

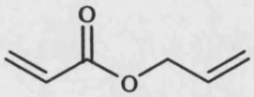


$C_{10}H_{10}O_2$
Mol. Wt.: 162.19

The title product was synthesised in a similar manner to allyl (2*E*)-3-phenyl-2-propenoate **98** and was obtained as a colourless oil (4.7 g, 29 mmol, 96% yield). R_f (15% Et_2O/ light petroleum) 0.42; υ_{max} (film)/cm^{-1} 3070, 2948, 1726, 1648, 1600, 1450, 1360, 1270, 1176, 1114, 1089, 1025, 970, 936, 714, 686; δ_H (270 MHz; $CDCl_3$) 4.81 (2H, dt, *J* 5.7, 1.4, O-CH_2), 5.28 (1H, dd, *J* 10.4, 1.5, H_2), 5.41 (1H, dd, *J* 17.3, 1.5, H_1), 6.03 (1H, ddt, *J* 17.3, 10.4, 5.3, H_3), 7.39-7.45 (2H, m, Ar-H), 7.51-7.57 (1H, m, Ar-H), 8.06 (2H, dd, *J* 8.4, 1.5, Ar-H).

Identical to literature data.[129]

Analysis of allyl acrylate 101



$C_6H_8O_2$
Mol. Wt.: 112.13

Obtained commercially, but for comparison δ_H (270 MHz; $CDCl_3$) 4.67 (2H, dt, *J* 5.7, 1.3, O-CH_2), 5.23-5.28 (2H, m, allyl =CH_2), 5.84 (1H, dd, *J* 10.3, 1.5, H_2), 5.88-6.03 (1H, m, allyl =CH), 6.15 (1H, dd, *J* 17.4, 10.3, H_3), 6.44 (1H, dd, *J* 17.4, 1.5, H_1).

General procedure (6) for palladium catalysed allylic substitution reactions

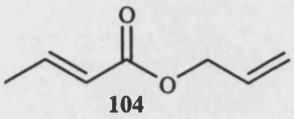
Into a flame dried round-bottom flask containing a stirring bead were placed $[(C_3H_5)PdCl]_2$ (5 mol% Pd) and PPh_3 (10 mol%). The flask was flushed with nitrogen and dry DCM (5 mL) was added. The pale yellow solution was stirred under nitrogen for 30 min and then added into a solution of the desired nucleophile (1 Eq., deprotonated with a suitable base prior to reaction) in DCM (5 mL). The allyl ester (1 Eq.) was then added to this and the reaction left at room temperature under nitrogen for 19 hours. The solvent was removed *in vacuo* and the allyl esters isolated by column chromatography (15% Et_2O/ light petroleum). In all cases the individual allyl esters were not isolated and the mixture analysed by ^1H NMR. It should be noted that, due to its volatility, when allyl acetate is utilised as an allyl source, only the cinnamate esters are isolated.

General procedure (7) for iridium catalysed allylic substitution reactions

Into a flame dried round-bottom flask containing a stirring bead were placed $[CODIrCl]_2$ (5 mol% Ir) and $P(OPh)_3$ (10 mol%). The flask was flushed with nitrogen and dry DCM (5 mL) was added. The solution was stirred under nitrogen for 30 min and then added into a solution of the desired nucleophile (1 Eq., deprotonated with a suitable base prior to reaction) in DCM (5 mL). The allyl ester (1 Eq.) was then added to this and the reaction left at room temperature under nitrogen for 19 hours. The solvent was removed *in vacuo* and the allyl esters isolated by column chromatography (15% Et_2O/ light petroleum). In all cases the individual allyl esters were not isolated

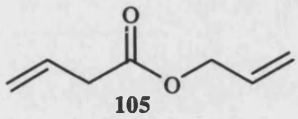
and the mixture analysed by ^{1}H NMR. It should be noted that, due to its volatility, when allyl acetate is utilised as an allyl source, only the cinnamate esters are isolated.

Synthesis of allyl (2*E*)-2-butenoate 104



104

$C_7H_{10}O_2$
Mol. Wt.: 126.15

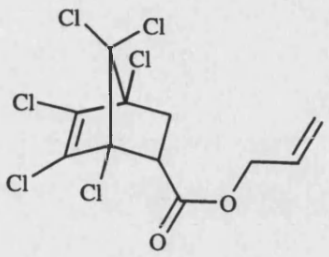


105

$C_7H_{10}O_2$
Mol. Wt.: 126.15

Crotonyl chloride (2.87mL, 30 mmol, 1 Eq.) was added dropwise to a stirred solution of allyl alcohol (2.04 mL, 30 mmol, 1 Eq.), anhydrous triethylamine (4.87 mL, 35 mmol, 1.2 Eq.) and catalytic DMAP in anhydrous diethyl ether (40 mL) at 0 °C under nitrogen. The reaction was stirred at this temperature for 20 min and then warmed to room temperature for 4 hours. The reaction was quenched with 2M HCl (10 mL) and extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by vacuum distillation to afford a mixture of regioisomeric esters as a colourless oil (2.1 g, 0.17 mmol, 55%). ^{1}H NMR analysis showed the ratio **104**:**105** to be 1:3.6 and was consistent with literature data.[83]

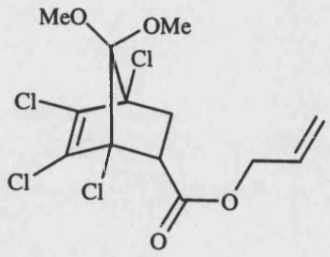
Synthesis of allyl -1,4,5,6,7,7-hexachloro-bicyclo[2.2.1]hept-5-ene-2-carboxylate 106



$C_{11}H_8Cl_6O_2$
Mol. Wt.: 384.90

1,2,3,4,5,5-Hexachlorocyclopentadiene (0.8 mL, 5 mmol, 1 Eq.) was added dropwise to a stirred solution of allyl acrylate (0.6 mL, 5 mmol, 1 Eq.) in toluene (15 mL) under nitrogen. The solution was heated to reflux for 18 hours at which time the solvent was removed *in vacuo*. The crude product was purified by column chromatography (5% Et_2O/ light petroleum) to give the desired product as a pale yellow oil (0.81 g, 2.1 mmol, 42%) R_f (15% Et_2O/ light petroleum) 0.66; υ_{max} (film)/cm^{-1} 2984.9, 2922.9, 2865.7, 1736.4, 1598.2, 1445.7, 1379.0, 1345.6, 1274.2, 1245.6, 1197.9, 1159.8, 1097.9, 1040.7, 978.7, 931.1, 916.8, 835.8, 816.7, 759.5; δ_H (270 MHz; $CDCl_3$) 2.58 (1H, dd, *J* 12.5, 4.2, C*H*HCCO$_2$Allyl), 2.70 (1H, dd, *J* 12.5, 8.8, CH*H*CCO$_2$Allyl), 3.65 (1H, dd, *J* 8.8, 4.2, CHCO$_2$Allyl), 4.62-4.65 (2H, m, OCH$_2$), 5.29 (1H, d, *J* 10.5, H_2), 5.39 (1H, d, *J* 17.2, H_1), 5.92 (1H, ddt, *J* 10.5, 17.2, 5.7, H_3); δ_c (67.9 MHz; $CDCl_3$) 38.2 (CH_2), 50.5 (CH), 66.8 (OCH_2), 78.4, 80.8, 105.0, 119.3 (=CH_2), 129.0 (=CCl), 131.0 (=CH), 132.4 (=CCl), 168.2 (C=O); *m/z* (EI) 383.9 (M^+, 7%), 348.9 (M-Cl, 17%), 272.9 (18%), 228.9 (21%), 83.9 (95%), 41.0 (C_3H_5, 100%); (Found: M^+ 381.8653. $C_{11}H_8Cl_6O_2$ requires 381.8655 based on 6 x ^{35}Cl) (Found: C, 33.9, H, 2.03. $C_{11}H_8Cl_6O_2$ requires C, 34.3, H, 2.09).

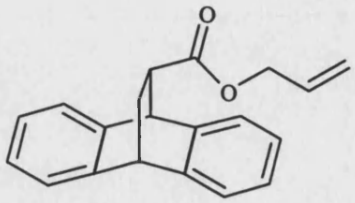
Synthesis of allyl bicyclo-1,4,5,6-pentachloro-7,7-dimethoxy[2.2.1]hept-5-ene-2-carboxylate 107



$C_{13}H_{14}Cl_4O_4$
Mol. Wt.: 376.06

1,2,3,4-Pentachloro-5,5-dimethoxycyclopentadiene (0.88 mL, 5 mmol, 1 Eq.) was added dropwise to a stirred solution of allyl acrylate (0.6 mL, 5 mmol, 1 Eq.) in xylenes (15 mL) under nitrogen. The solution was heated to reflux for 18 hours at which time the solvent was removed *in vacuo*. The crude product was purified by column chromatography (15% Et_2O/ light petroleum) to give the desired product as a pale yellow oil (0.56 g, 1.5 mmol, 30%); R_f (15% EtOAc/ light petroleum) 0.46; υ_{max} (film)/cm^{-1} 2975.8, 2995.3, 2837.6, 1731.4, 1603.4, 1444.7, 1373.0, 1337.1, 1280.8, 1260.3, 1188.6, 1157.9, 1122.1, 1096.4, 1040.1, 988.9, 927.5, 789.2, 881.4, 825.0; δ_H (270 MHz; $CDCl_3$) 2.28 (1H, dd, *J* 11.7, 4.2, C*H*HCCO$_2$Allyl), 2.53 (1H, dd, *J* 11.7, 9.3, CH*H*CCO$_2$Allyl), 3.47 (1H, dd, *J* 9.3, 4.2, CHCO$_2$Allyl), 3.56 (3H, s, OMe), 3.62 (3H, s, OMe), 4.56 (1H, dd, *J* 13.3, 6.0, OC*H*H), 4.64 (1H, dd, *J* 13.3, 6.0, OCH*H*), 5.26 (1H, dd, *J* 10.4, 1.3, H_2), 5.36 (1H, dd, *J* 17.2, 1.3, H_1), 5.91 (1H, ddt, *J* 17.2, 10.4, 6.0, H_3); δ_c (100.6 MHz; $CDCl_3$) 38.9 (CH_2), 50.5 (CH), 51.7 (OMe), 52.7 (OMe), 66.1 (OCH_2), 74.0, 76.8, 111.8, 118.6 (=CH_2), 127.8 (=CCl), 130.3 (=CCl), 131.3 (=CH), 169.1 (C=O); m/z (FAB$^+$) 376.9 (M^+, 30%), 338.9 (M-Cl, 100%); (Found: M^+ 373.9653. $C_{13}H_{14}Cl_4O_4$ requires 373.9646 based on 4 x ^{35}Cl).

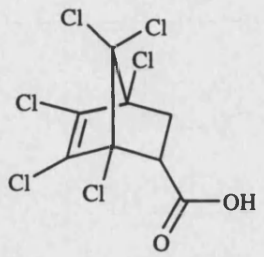
Synthesis of allyl 9,10-dihydro-9,10-ethanoanthracene-11-carboxylate 108



$C_{20}H_{18}O_2$
Mol. Wt.: 290.36

Allyl acrylate (0.6 mL, 5 mmol, 1 Eq.) was added dropwise to a stirred solution of anthracene (0.89 g, 5 mmol, 1 Eq.) in mixed xylenes (15 mL) under nitrogen. The solution was heated to reflux for 18 hours at which time the solvent was removed *in vacuo*. The crude product was purified by column chromatography (5% Et_2O/ light petroleum) to give the desired product as a white solid (35 mg, 0.1 mmol, 2%); R_f (15% Et_2O/ light petroleum) 0.30; δ_H (400 MHz; $CDCl_3$) 2.00 (1H, ddd, *J* 12.7, 10.5, 2.5, C*H*HCCO_2Allyl), 2.18 (1H, ddd, *J* 12.7, 4.7, 2.5, CH*H*CCO_2Allyl), 2.91 (1H, ddd, *J* 10.5, 4.7, 2.3, C*H*CO_2Allyl), 4.34 (1H, t, *J* 2.5, C*H*CH_2CO_2Allyl), 4.46-4.50 (2H, m, OCH_2), 4.70 (1H, d, *J* 2.3, C*H*CHCO_2Allyl), 5.21 (1H, dd, *J* 10.5, 1.4, H_2), 5.24 (1H, dd, *J* 17.2, 1.4, H_1), 5.84 (1H, ddt, *J* 17.2, 10.5, 5.9, H_3), 7.05-7.20 (4H, m, Ar-H), 7.22-7.33 (4H, m, Ar-H); δ_c (100.6 MHz; $CDCl_3$) 30.8 (CH_2), 43.9 (CH), 44.1 (CH), 46.9 (CH), 65.4 (CH_2), 118.1 (=CH_2), 123.1, 123.3, 123.5, 124.7, 125.6, 125.7, 126.0, 126.1, 132.1 (=CH), 139.8, 142.2, 143.5, 143.8, 172.9 (C=O); *m/z* (EI) 290.1 (M^+, 25%), 178 (96%), 83.9 (100%), 46.9 (24%); (Found: M^+ 290.1309. $C_{20}H_{18}O_2$ requires 290.1307).

Synthesis of 1,4,5,6,7,7-hexachloro-bicyclo[2.2.1]hept-5-ene-2-carboxylate 109

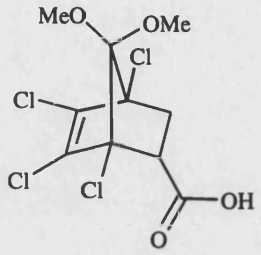


$C_8H_4Cl_6O_2$
Mol. Wt.: 344.83

1,2,3,4,5,5-Hexachlorocyclopentadiene (0.8 mL, 5 mmol, 1 Eq.) was added dropwise to a stirred solution of acrylic acid (0.34 mL, 5 mmol, 1 Eq.) in toluene (15 mL) under nitrogen. The solution was heated to reflux for 18 hours. The solution was cooled and washed with 2M NaOH (3 x 10 mL). The aqueous washings were acidified with 2M HCl and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The resultant crude product was recrystalised from DCM/ hexane to give the desired product as a white solid (0.98 g, 2.8 mmol, 57%); Mp 173-176 °C; R_f (20% EtOAc/ light petroleum) 0.09; υ_{max} (nujol)/cm^{-1} 2856.2, 2637.0, 2541.7, 1703.0, 1603.0, 1417.1, 1326.6, 1283.7, 1245.6, 1212.2, 1150.3, 1097.9, 1074.0, 1016.9, 978.7, 921.5, 883.4, 826.2, 807.2, 740.5; δ_H (400 MHz; $CDCl_3$) 2.55 (1H, dd, *J* 4.0, 12.7, C*H*H), 2.73 (1H, dd, *J* 12.7, 9.0, CH*H*), 3.69 (1H, dd, *J* 9.0, 4.0, CH), 10.29 (1H, brd s, OH); δ_c (100.6 MHz; $CDCl_3$) 38.2 (CH_2), 50.3 (CH), 78.2, 80.5, 102.2, 129.2 (=CCl), 132.4 (=CCl), 173.8 (C=O); *m/z* (EI) 343.9 (M^+, 14%), 308.9 (M-HCl, 100%), 271.9 (M-2HCl, 27%), 229.0 (M-CO_2Cl_2); (Found: M^+ 341.83464. $C_8H_4C_{l6}O_2$ requires 341.83424 based on 6 x ^{35}Cl).

Identical to literature data.[130]

Synthesis of 1,4,5,6-pentachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-5-ene-2-carboxylate 110

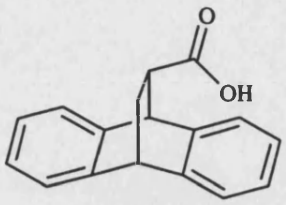


$C_{10}H_{10}Cl_4O_4$
Mol. Wt.: 335.99

1,2,3,4-Pentachloro-5,5-dimethoxy-cyclopentadiene (0.88 mL, 5 mmol, 1 Eq.) was added dropwise to a stirred solution of acrylic acid (0.34 mL, 5 mmol, 1 Eq.) in xylenes (15 mL) under nitrogen. The solution was heated to reflux for 18 hours. The solution was cooled and washed with 2M NaOH (3 x 10 mL). The aqueous washings were acidified with 2M HCl and extracted with DCM (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The resultant crude product was recrystalised from diethyl ether/ hexane to give the desired product as a white solid (1.21 g, 3.6 mmol, 72%); Mp 169-172 °C (lit.[131] 165-166 °C); υ_{max} (nujol)/cm^{-1} 2989.6, 2956.3, 2851.4, 2637.0, 2551.2, 1703.0, 1607.7, 1441.0, 1336.1, 1274.2, 1245.6, 1193.2, 1131.2, 1107.4, 1055.0, 997.8, 921.5, 864.4, 788.1, 688.1; δ_H (270 MHz; $CDCl_3$) 2.25 (1H, dd, *J* 11.7, 4.0, C*H*H), 2.54 (1H, dd, *J* 11.7, 9.5, CH*H*), 3.49 (1H, dd, *J* 9.5, 4.0, CH), 3.56 (3H, s, OMe), 3.62 (3H, s, OMe), 10.76 (1H, brd s, OH); δ_C (67.9 MHz; $CDCl_3$) 30.9 (CH_2), 50.4 (CH), 51.8 (OMe), 52.8 (OMe), 74.0, 76.7, 111.9, 127.8 (=CCl), 130.7 (=CCl), 175.9 (C=O); *m/z* (FAB^+) 336.0 (MH^+, 20%), 298.9 (M-Cl, 100%); *m/z* (FAB^-) 334.9 (M-H, 100%), 188.0 ($C_9H_6O_2Cl$, 30%); (Found: M^+ 333.9337. $C_{10}H_{10}Cl_4O_4$ requires 333.9333 based on 4 x ^{35}Cl) (Found: C, 35.7, H, 3.00. $C_{10}H_{10}Cl_4O_4$ requires C, 35.8, H, 3.00).

Identical to literature data.[131]

Synthesis of 9,10-dihydro-9,10-ethanoanthracene-11-carboxylate 111



$C_{17}H_{14}O_2$
Mol. Wt.: 250.29

Acrylic acid (0.34 mL, 5 mmol, 1 Eq.) was added dropwise to a stirred solution of anthracene (0.89 g, 5 mmol, 1 Eq.) in xylenes (15 mL) under nitrogen. The solution was heated to reflux for 18 hours. The solution was cooled and washed with 2M NaOH (3 x 10 mL). The aqueous washings were acidified with 2M HCl and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The resultant crude product was purified by column chromatography (15% Et_2O/ light petroleum) to give the desired product as a white solid (0.95 g, 3.8 mmol, 76%); Mp 188-190 °C (lit.[132] 189-192 °C); R_f (20% EtOAc/ light petroleum) 0.14; υ_{max} (nujol)/cm^{-1} 2922.6, 2858.0, 2722.8, 1708.2, 1458.7, 1408.6, 1377.1, 1324.7, 1296.3, 1248.1, 1232.6, 1158.3, 1115.5, 1028.6, 943.8, 927.9, 760.1, 738.3, 631.3; δ_H (400 MHz; $CDCl_3$) 2.00 (1H, ddd, *J* 12.9, 10.5, 2.5, C*H*H), 2.10 (1H, ddd, *J* 12.9, 5.0, 2.5, CH*H*), 2.89 (1H, ddd, *J* 10.5, 5.0, 2.7, *H*CCO_2H), 4.33 (1H, t, *J* 2.5, C*H*CH_2CO_2H), 4.66 (1H, d, *J* 2.7, C*H*$CHCO_2H$), 5.94-6.97 (4H, m, Ar-H), 7.05-7.13 (4H, m, Ar-H), 11.38 (1H, brd s, OH); δ_C (100.6 MHz; $CDCl_3$) 30.5 (CH_2), 43.7 (CH), 43.9 (CH), 46.4 (CH), 122.9, 123.2, 123.4, 124.8, 125.5, 125.6, 125.9, 126.0, 139.3, 142.0, 143.3, 143.4, 178.9 (C=O); *m/z* (EI) 251.1

(M+H, 5%), 178.1 (Anthracene, 100%); (Found: M^+ 250.0994. $C_{17}H_{14}O_2$ requires 250.0994) (Found: C, 81.6, H, 5.70. $C_{17}H_{14}O_2$ requires C, 81.6, H, 5.64).

Identical to literature data.[132]

Diels-Alder reaction between acrylic acid and anthracene in the presence of various bases

A solution of anthracene (0.89 g, 5 mmol, 1 Eq.) in toluene (2 mL) was added to a stirred solution of acrylic acid (0.34 mL, 5 mmol, 1 Eq.) and a suitable base (1.1 Eq.) in toluene (5 mL). The solution was heated to reflux for 18 hours, cooled and washed with 2M NaOH (3 x 10 mL). The aqueous washings were acidified with 2M HCl and extracted with DCM (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. Analysis of the crude ^1H NMR showed less than 5% conversion to the desired product.

Diels-Alder reaction between acrylic acid and cyclopentadiene in the presence of various bases

Cyclopentadiene monomer (2.06 mL, 25 mmol, 5 Eq.) was added to a stirred solution of acrylic acid (0.34 mL, 5 mmol, 1 Eq.) and a suitable base (1.1 Eq.) in DCM (5 mL). The solution was stirred at room temperature for 24 hours and evaporated to dryness. Analysis of the crude ^1H NMR showed no conversion to the desired product.

Diels-Alder reaction between acrylic acid and cyclopentadiene in the presence of palladium

Into an evacuated round-bottom flask containing a stirring bead were placed Pd_2dba_3 (22 mg, 0.025 mmol, 5 mol% Pd) and PPh_3 (26 mg, 0.1 mmol, 10 mol%). The flask was flushed with nitrogen and dry DCM (5 mL) was added. The pale yellow solution was stirred under nitrogen for 30 min and then allyl acrylate (0.12 mL, 1 mmol, 1 Eq.) and cyclopentadiene monomer (0.41 mL, 5 mmol, 5 Eq.) were added. The reaction was stirred at room temperature for 18 hours and evaporated to dryness. Column chromatography (15% Et_2O/ light petroleum) gave allyl bicyclo [2.2.1] hept-5-ene-2-carboxylate **103** as a colourless oil (106 mg, 0.77 mmol, 77%).

General procedure (8) for the attempted full catalytic cycle

Into an evacuated round-bottom flask containing a stirring bead were placed $[(C_3H_5)PdCl]_2$ (9.1 mg, 0.025 mmol, 5 mol% Pd) and PPh_3 (26 mg, 0.1 mmol, 10 mol%). The flask was flushed with nitrogen and dry DCM (5 mL) was added. The pale yellow solution was stirred under nitrogen for 30 min and then added into a solution of the desired carboxylate generated *in situ* by prior treatment of acrylic acid (68 μL, 1 mmol, 1 Eq.) with DBU (0.17 mL, 1.1 mmol, 1.1 Eq.). Allyl acetate (0.11 mL, 1 mmol, 1 Eq.) was added and the solution was left at room temperature for 3 hours. Cyclopentadiene monomer (0.41 mL, 5 mmol, 5 Eq.) was added and the reaction left at room temperature for a further 15 hours when it was diluted with DCM and washed with 2M HCl. The aqueous phase was extracted with DCM and the combined organic phases dried over $MgSO_4$ and evaporated to dryness. The crude oil is purified by column chromatography (10% EtOAc/ light petroleum). Analysis of the

^{1}H NMR of all isolated fractions showed that no bicyclo [2.2.1] hept-5-ene-2-carboxylic acid **83** was formed.

Attempted sequential Diels-Alder and allylic substitution reactions

Into an evacuated round-bottom flask containing a stirring bead were placed $[(C_3H_5)PdCl]_2$ (9.1 mg, 0.025 mmol, 5 mol% Pd) and PPh_3 (26 mg, 0.1 mmol, 10 mol%). The flask was flushed with nitrogen and dry DCM (5 mL) was added. The pale yellow solution was stirred under nitrogen for 30 min and then allyl acrylate (0.12 mL, 1 mmol, 1 Eq.) and cyclopentadiene monomer (0.41 mL, 5 mmol, 5 Eq.) were added. The reaction was stirred at room temperature for 24 hours and then transferred *via* syringe to a stirred solution of the desired nucleophile generated *in situ* by the prior treatment of cinnamic acid (0.15 g, 1 mmol, 1Eq.) with DBU (0.16 mL, 1.1 mmol, 1 Eq.). The reaction was stirred for a further 24 hours and the solvent was removed *in vacuo*. Analysis of the crude ^{1}H NMR showed no allyl cinnamate **98** had been produced.

Synthesis of palladium complex 1

Into an evacuated round-bottom flask containing a stirring bead were placed Pd_2dba_3 (1.01 g, 0.11 mmol, 1 Eq. Pd) and PPh_3 (0.115 g, 0.44 mmol, 2 Eq.). The flask was flushed with nitrogen and dry DCM (20 mL) was added. The pale yellow solution was stirred under nitrogen for 30 min and then 1,2,3,4,5,5-hexachlorocyclopentadiene (0.18 mL, 1.1 mmol, 5 Eq.). An instantaneous darkening of colour was observed. After 6 hours the solution had turned very dark. The solvent was removed *in vacuo* to

give a mixture of red and black precipitates. Diethyl ether was added to dissolve the red precipitate. The solution was decanted *via* cannula and recrystalised by layering hexane. The identity of the palladium complex **1** was disclosed by the determination of its X-ray crystal structure (**Appendix 2**).

General procedure (9) for the basic cleavage of allyl esters

Solid KOH was added to a stirred solution of allyl bicyclo [2.2.1] hept-5-ene-2-carboxylate **103** (0.18 g, 1 mmol, 1 Eq.) in MeOH (8 mL) and water (2 mL) until the solution reached ~pH 11. The solution was heated to reflux for 2 hours, or until judged to be complete by TLC analysis. The solvent was removed *in vacuo* and partitioned between water (20 mL) and diethyl ether (20 mL). The aqueous layer was acidified with 2M HCl and washed with diethyl ether (2 x 20 mL). The combined organic extracts were dried over MgSO4, filtered and concentrated to give the desired bicyclo [2.2.1] hept-5-ene-2-carboxylic acid **83** as an oil (99 mg, 0.72 mmol, 72%).

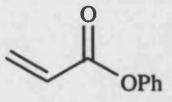
This methodology could be adapted to the attempted full cycles by removing the solvent *in vacuo* once reaction is complete and then carrying out the basic hydrolysis reaction on the crude reaction mixture. Column chromatography (15% Et_2O/ light petroleum) allows isolation of the desired bicyclo [2.2.1] hept-5-ene-2-carboxylic acid **83**, although this is still impure as judged by ^1H NMR analysis.

5.3 Experimental for Chapter 3

General procedure (10) for the synthesis of phenyl esters

A solution of the appropriate acid chloride (53 mmol, 1 Eq.) in diethyl ether (10 mL) was added dropwise to a stirred solution of phenol (4.99g, 53 mmol, 1 Eq.) and triethyl amine (8.1 mL, 58 mmol, 1.1 Eq.) in diethyl ether (10 mL) at 0 °C under nitrogen. The reaction was stirred at this temperature for 10 min and then warmed to room temperature for 90 min. The reaction was quenched with saturated ammonium chloride (30 mL) and the organic layer was washed with saturated ammonium chloride (2 x 30 mL) and water (1 x 30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*.

Phenyl Acrylate 118a

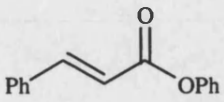


$C_9H_8O_2$
Mol. Wt.: 148.16

Purified by vacuum distillation to give the desired product as a colourless oil (6.1 g, 41 mmol, 78%); Bp 98 °C/ 24 mmHg; R_f (10% EtOAc/ light petroleum) 0.55; δ_H (300 MHz; $CDCl_3$) 5.95 (1H, d, *J* 10.4, H_2), 6.29 (1H, dd, *J* 17.3, 10.4, H_3), 6.57 (1H, d, *J* 17.3, H_1), 7.09-7.15 (2H, m, Ar-H), 7.17-7.24 (1H, m, Ar-H), 7.33-7.40 (2H, m, Ar-H); δ_c (75.5 MHz; $CDCl_3$); *m/z* (EI) 148.0 (M^+, 27%), 94.0 (M-C_3H_2O, 18%), 55.0 (M-OPh, 100%); (Found: M^+ 148.0523. $C_9H_8O_2$ requires 148.0524).

Commercially available.

Phenyl (2*E*)-3-phenyl-2-propenoate 122a

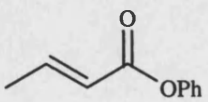


$C_{15}H_{12}O_2$
Mol. Wt.: 224.25

Purified by column chromatography (10% EtOAc/ light petroleum) to give the desired product as a white solid (9.9 g, 44 mmol, 83%); Mp 73-75 °C (lit.[133] 75-76 °C); R_f (10% EtOAc/ light petroleum) 0.30; HPLC (AD column, 95:5 Hexane:propan-2-ol, 1.0 mL/ min) t_r = 9.9 min; υ_{max} (nujol)/cm^{-1} 3051.6, 2908.6, 1717.3, 1641.1, 1588.7, 1483.8, 1445.7, 1312.3, 1207.5, 1183.6, 1140.7, 1064.5, 1016.9, 974.0, 850.1, 769.1, 730.9, 692.8; δ_H (400 MHz; $CDCl_3$) 6.63 (1H, d, *J* 16.0, =$CHCO_2$OPh), 7.16-7.19 (2H, m, Ar-H), 7.56-7.58 (2H, m, Ar-H), 7.87 (1H, d, *J* 16.0, =CHAr); δC (100.6 MHz; $CDCl_3$) 117.1, 121.5, 125.6, 128.1, 128.8, 129.3, 130.5, 134.0, 146.3, 150.6, 165.1 (C=O); *m/z* (FAB) 225.2 (M+H, 36%), 131.1 (M-OPh, 100%), 102.9 (M-CO_2Ph, 10%); (Found: M^+ 225.0914. $C_{15}H_{12}O_2$ Requires 224.0837) (Found: C, 80.4, H, 5.43. $C_{15}H_{12}O_2$ requires C, 80.3, H, 5.39).

Identical to literature data.[133]

Synthesis of phenyl (2*E*)- 2-butenoate 120a



$C_{10}H_{10}O_2$
Mol. Wt.: 162.19

Concentrated sulphuric acid (0.4 mL) was added to a stirred solution of crotonic acid (10 g, 116 mmol, 1 Eq.), phenol (116 mmol, 10.9 g, 1 Eq.) and hydroquinone in toluene (100 mL). The reaction was heated to reflux with azeotropic removal of water (Dean-Stark conditions) for 24 hours under nitrogen. The solvent was removed *in vacuo* and the resultant oil partitioned between diethyl ether (40 mL) and 10% NaOH solution (40 mL). The organic layer was washed with 10% NaOH (2 x 30 mL), water (2 x 30 mL) and brine (2 x 30 mL), dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by vacuum distillation to give the desired product as a colourless oil (9.4 g, 58 mmol, 50%); Bp 110 °C/ 8 mmHg; R_f (10% EtOAc/ light petroleum) 0.36; υ_{max} (film)/cm^{-1} 3037.3, 2975.8, 2945.1, 2914.4, 1731.4, 1654.6, 1598.3, 1495.9, 1449.8, 1311.5, 1291.0, 1255.2, 1198.9, 1152.8, 1101.6, 1019.6, 968.4, 922.3, 891.6, 830.2, 804.6, 779.0, 727.7; δ_H (300 MHz; $CDCl_3$) 1.89 (3H, dd, *J* 1.7, 6.9, CH_3), 6.02 (1H, dq, *J* 15.5, 1.7, =CH), 7.08-7.14 (2H, m, Ar-H), 7.15-7.21 (2H, m, Ar-H & =CH), 7.31-7.38 (2H, m, Ar-H); *m/z* (EI) 162.1 (M^+, 12%), 94.0 (11%), 69.0 (100%), 41.0 (27%); (Found: M^+ 162.06736. $C_{10}H_{10}O_2$ requires 162.06808).

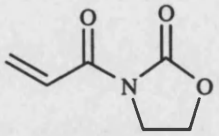
Identical to literature data.[134]

The non-conjugated isomer is also present (6% by ^1H NMR analysis); δ_H (300 MHz; $CDCl_3$) 2.18 (1H, dd, *J* 7.3, 1.8, CH2), 6.41-6.45 (1H, m, CH), 7.08-7.14 (3H, m, $=CH_2$ & Ar-H), 7.15-7.27 (2H, m, Ar-H), 7.31-7.38 (2H, m, Ar-H).

General procedure (11) for the synthesis of α,β-unsaturated oxazolidinyl substrates

2-Oxazolidinone (2.5 g, 29 mmol, 1.04 Eq.) was added portionwise to a stirred suspension of NaH (1.3 g (60% w/w in mineral oil), 32 mmol, 1.1 Eq.) in DCM (30 mL) at 0 °C under nitrogen. This was allowed to stir at 0 °C for 1 h when a solution of the requisite acid chloride (28 mmol, 1 Eq.) was added slowly *via* cannula. The reaction was allowed to warm to room temperature overnight. The reaction was quenched by adding saturated ammonium chloride (50 mL), extracted with DCM (3 x 40 mL) and the organic extracts washed with saturated ammonium chloride (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

Oxazolidinyl acrylate 119a



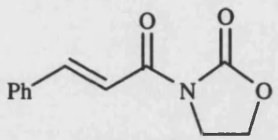
$C_6H_7NO_3$
Mol. Wt.: 141.12

Purified by recrystallisation from DCM/ hexane to give the desired product as a white solid (7.0 g, 50 mmol, 71%); Mp 81-83 °C (lit.[135] 80-81 °C); R_f (35% EtOAc/ light petroleum) 0.15; HPLC (OD column, 94:6 Hexane:propan-2-ol) t_r = 31.5 min; GC (β-dex column, 140 °C) t_r = 35.6 min; δ_H (270 MHz; $CDCl_3$) 4.10 (2H, t, *J* 8.0, OCH_2), 4.46 (2H, t, *J* 8.0, NCH_2), 5.91 (1H, dd, *J* 10.4, 1.8, H_2), 6.56 (1H, dd, *J* 17.0, 1.8, H_1), 7.50 (1H, dd, *J* 17.0, 10.4, H_3); δ_C (100.6 MHz; $CDCl_3$) 42.6 (OCH_2), 62.1 (NCH_2), 126.8 (=CH), 131.5 ($=CH_2$), 153.2 (C=O), 164.8 (C=O); *m/z* (FAB) 142.0 (MH^+,

100%), 111.1 (23%), 97.1 (42%), 70.0 (14%); (Found: MH^+ 142.05024. $C_6H_7NO_2$ requires 142.05042).

Identical to literature data.[135]

Oxazolidinyl (2*E*)-3-phenyl-2-propenoate 123a

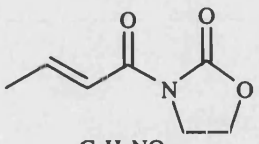


$C_{12}H_{11}NO_3$
Mol. Wt.: 217.22

Purified by column chromatography (20% EtOAc/ light petroleum) to give the desired product as a white solid (4.7 g, 22 mmol, 77%); Mp 151-152 °C (lit.[135] 151-152 °C); R_f (50% EtOAc/ light petroleum) 0.37; υ_{max} (nujol)/cm^{-1} 3257.5, 3093.6, 2934.9, 1757.0, 1716.1, 1675.1, 1613.7, 1475.4, 1444.7, 1398.6, 1357.6, 1219.4, 1209.1, 1106.7, 1040.1, 978.7, 866.0, 768.7, 748.2, 707.3, 676.5; δ_H (400 MHz; $CDCl_3$) 4.14 (2H, t, *J* 8.0, OCH_2), 4.46 (2H, t, *J* 8.0, NCH_2), 7.39-7.42 (3H, m, Ar-H), 7.60-7.65 (2H, m, Ar-H), 7.86 (1H, d, *J* 15.8, =CH), 7.92 (1H, d, *J* 15.8, =CH); δ_C (75.5 MHz; $CDCl_3$) 43.2 (OCH_2), 62.5 (NCH_2), 90.8 (CH), 116.9 (CH), 120.9 (CH), 129.3 (CH), 131.1 (Ar-C), 134.9 (CH), 146.7 (C=O), 165.8 (C=O); *m/z* (FAB); (Found: M^+. $C_{12}H_{11}NO_3$ requires) (Found: C, 66.2, H, 5.11, N, 6.3. $C_{12}H_{11}NO_3$ requires C, 66.4, H, 5.11, N, 6.5).

Identical to literature data.[135]

Synthesis of oxazolidinyl (2*E*)- 2-butenoate 120a



$C_7H_9NO_3$
Mol. Wt.: 155.15

n-BuLi (33 mL (1.5 M solution in hexanes), 50 mmol, 1 Eq.) was added dropwise to a stirred solution of 2-oxazolidinone (4.4 g, 50 mmol, 1 Eq.) in THF (100 mL) at –78 °C under nitrogen. The reaction was stirred for 15 min at this temperature when crotonyl chloride (5.9 mL (technical grade), 55 mmol, 1.1 Eq.) was added slowly. The reaction was stirred at this temperature for 30 min and at 0 °C for a further 15 min when the reaction was quenched by addition of excess saturated ammonium chloride. The solvent was concentrated *in vacuo* to give a pale yellow oil, which was diluted with diethyl ether (50 mL). The organic layer was washed with saturated sodium bicarbonate (3 x 30 mL) and brine (2 x 30 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (20% EtOAc/ light petroleum to 35% EtOAc/ light petroleum) to give the desired product as viscous oil; (3.3 g, 21 mmol, 43%); R_f (50% EtOAc/ light petroleum) 0.37; υ_{max} (film)/cm^{-1} 2960.5, 2929.7, 1777.5, 1685.4, 1639.3, 1480.5, 144.7, 1383.2, 1342.3, 1296.2, 1219.4, 1122.1, 1086.2, 1040.1, 963.3, 922.3, 830.2, 758.5, 732.9, 702.1; δ_H (300 MHz; $CDCl_3$) 1.96 (3H, d, *J* 5.4, CH_3), 4.07 (2H, t, *J* 8.0, OCH_2), 4.43 (2H, t, *J* 8.0, NCH_2), 7.11-7.29 (2H, m, =CH).

Identical to literature data.[135]

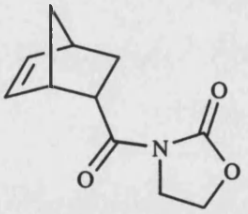
Calibration of HPLC for rate of Diels-Alder reaction of oxazolidinyl acrylate 119a

Prior to the rate reaction samples of 10, 50, 100, 150 and 300μg/ mL of both starting oxazolidinyl acrylate **119a** and the Diels-Alder adduct **119c** were analysed by HPLC. At these low concentrations, the relationship between concentration and absorbance is approximately linear. By determining the ratio of the gradients of the lines for oxazolidinyl acrylate **119a** and Diels-Alder adduct **119c**, the ratio of absorbance for the two adducts can be determined. As this ratio is constant, the percentage conversion can be determined using the equation:

Percentage conversion= (Area **199c**/ Mol Wt. **119c**)/((Area **119c**/ Mol Wt. **119c**) + ((Area **119a**/ Ratio))/ Mol Wt. **119a**))

In this instance Ratio = 2.8

Synthesis of 3-(bicyclo[2.2.1]hept-5-ene-2-ylcarbonyl)-2-oxazolidinone 119c



$C_{11}H_{13}NO_3$
Mol. Wt.: 207.23

Freshly prepared cyclopentadiene monomer (0.41 mL, 5 mmol, 5 Eq.) was added dropwise to a stirred solution of oxazolidinyl acrylate **119a** (0.14 g, 1 mmol, 1 Eq.) in DCM (2 mL) at room temperature under nitrogen. Aliquots were taken at regular intervals and conversion determined by HPLC analysis after prior calibration with known standards. Upon completion saturated ammonium chloride (15 mL) was added

to quench the reaction and was washed with DCM (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (33% EtOAc/ light petroleum to 35% EtOAc/ light petroleum) to give the desired product as a white solid (0.17 g, 0.84 mmol, 84%); Mp 81-83 °C; R_f (33% EtOAc/ light petroleum) 0.22; HPLC (OD column, 94:6 Hexane:propan-2-ol, 1 mL/ min) t_r = 23.4 min, 24.2 min (*exo*), 25.6 min, 28.7 min (*endo*); υ_{max} (film)/cm^{-1} 2975.8, 2934.9, 1762.2, 1695.6, 1485.6, 1398.6, 1357.6, 1285.9, 1209.1, 1122.1, 1045.2, 994.0, 937.7, 860.9, 768.7, 702.1; δ_H (400 MHz; $CDCl_3$) 1.40-1.60 (3H, m, CH & CH_2), 1.93-1.99 (1H, m, CH), 2.95 (1H, brd s, CH), 3.32 (1H, brd s, CH), 3.92- 4.06 (3H, m, CH & OCH_2), 4.39- 4.43 (2H, m, NCH_2), 5.87- 5.89 (1H, m, =CH *endo*), 6.18 (2H, m, brd s, =CH *exo*), 6.24-6.26 (1H, m, =CH *endo*); δ_C (100.6 MHz; $CDCl_3$) 30.0 (CH_2), 43.2 (CH), 43.3 (CH), 43.6 (OCH_2), 46.7 (CH), 50.5 (CH_2), 62.3 (NCH_2), 131.8 (=CH), 138.3 (=CH), 145.9 (C=O), 174.8 (C=O); *m/z* (FAB) 208.1 (MH^+, 100%), 164.0 (4%), 142.0 (87%), 133.0 (7%), 111.1 (8%), 97.1 (16%), 88.0 (11%), 80.0 (6%), 73.0 (15%), 56.0 (6%); (Found: M^+ 207.08994 $C_{11}H_{13}NO_2$ requires 207.08954).

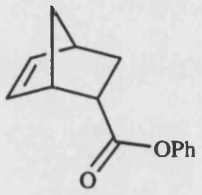
Identical to literature data.[101]

General procedure (12) for the $Yb(OTf)_3$ catalysed Diels-Alder reaction of α,β-unsaturated phenyl and oxazolidinyl substrates

Into an evacuated round-bottom flask containing a stirring bead were placed $Yb(OTf)_3$ (62 mg, 0.1 mmol, 10 mol%) and the appropriate substrate (1 mmol, 1 Eq.). The flask was flushed with nitrogen and dry DCM (5 mL) was added. The requisite diene (5

mmol, 5 Eq.) was added and the reaction was left for 18 h under nitrogen at room temperature. The reaction was quenched with water (5 mL), extracted with DCM (2 x 5 mL), dried over $MgSO_4$ and evaporated to dryness. ^1H NMR analysis of the crude reaction mixture allowed the conversion to be determined. Reactions that had not proceeded to completion, but showed some indication of product formation were purified by column chromatography to give the pure cycloadducts.

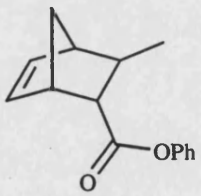
Phenyl bicyclo[2.2.1]hept-5-ene-2-carboxylate 118c



$C_{14}H_{14}O_2$
Mol. Wt.: 214.26

Title compound was isolated as a colourless oil. (214 mg, 1 mmol, 100%); δ_H (400 MHz; $CDCl_3$) 1.36-1.65 (3H, m, CH & CH_2), 1.84-2.01 (1H, m, CH), 2.97 (2H, m, CH_2), 3.42 (1H, m, CH), 5.92- 5.95 (1H, m, =CH *endo*), 6.28 (2H, m, brd s, =CH *exo*), 6.31-6.35 (1H, m, =CH *endo*).

Phenyl–3-methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate 120c

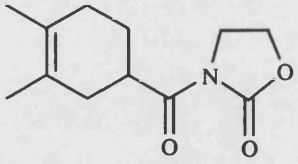


$C_{15}H_{16}O_2$
Mol. Wt.: 228.29

Isolated as a pale yellow oil (36 mg, 0.16 mmol, 16%); δ_H (400 MHz; $CDCl_3$) 1.02 (3H, d, *J* 6.5, CH_3), 1.24 (3H, d, *J* 6.6, Me), 1.45-1.85 (3H, m, CH & CH_2), 2.56-2.85

(2H, m, CH), 3.37-3.41 (1H, m, CH), 6.05-6.12 (1H, m, =CH), 6.23-6.31 (1H, m, =CH), 6.90-7.41 (5H, m, Ar-H).

3-[3,4-Dimethylcyclohex-3-en-1-ylcarbonyl]-2-oxazolidinone 119b

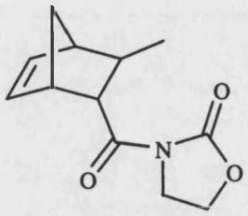


$C_{12}H_{17}NO_3$
Mol. Wt.: 223.27

The title compound was isolated as a viscous oil (223 mg, 1 mmol, 100%) R_f (20% EtOAc/ light petroleum) 0.14; υ_{max} (film)/cm^{-1} 2980.9, 2929.7, 2873.4, 1777.5, 1680.2, 1475.4, 1378.1, 1362.7, 1280.8, 1188.6, 1111.6, 1050.4, 999.2, 937.7, 814.8, 758.5, 712.4; δ_H (300 MHz; $CDCl_3$) 1.57-1.69 (1H, m, CH), 1.62 (6H, s, CH_3), 1.88-2.22 (5H, m, CH & CH_2), 3.64-3.72 (1H, m, CH), 4.03 (2H, t, *J* 8.2, O-CH_2), 4.42 (2H, t, *J* 8.2, NCH_2); δ_C (75.5 MHz; $CDCl_3$) 19.2, 19.3 (CH_3), 26.5, 31.5, 33.8 (CH_2), 39.4 (CH), 43.2, 62.3, (CH_2), 124.0, 125.6 (C=), 153.6, 176.9 (C=O); *m/z* (EI); 223.1 (M^+, 27%), 136.1 (M-$C_3H_5NO_2$, 83%), 108.1 (M- $C_4H_5NO_3$, 100%), 93.1 (86%), 77.0 (17%), 67.1 (23%), 55.0 (17%), 43.0 (37%), 26.7 (16%); (Found: M^+ 223.1205. $C_{12}H_{17}NO_3$ Requires 223.1208).

Identical to literature data.[136]

3-(3-methylbicylco[2.2.1]hept-5-ene-2-ylcarbonyl)-2-oxazolidinone 121c

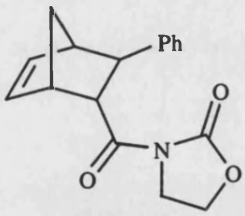


$C_{12}H_{15}NO_3$
Mol. Wt.: 221.25

The title compound was isolated as a pale yellow oil (221 mg, 1 mmol, 100%) δ_H (300 MHz; $CDCl_3$) 0.86 (3H, d, *J* 6.8, CH_3 *exo*), 1.13 (3H, d, *J* 7.1, CH_3 *endo*), 1.36-1.41 (1H, m, CH), 1.64-1.72 (1H, m, CH), 2.06-2.14 (2H, m, CH_2 *exo*), 2.53 (1H, brd d, CH *endo*), 2.64-2.74 (1H, m, CH), 2.86-2.89 (1H, m, CH), 3.28 (1H, brd s, CH *endo*), 3.53 (1H, dd, *J* 3.4, 4.4, CH), 3.89-4.08 (2H, m, OCH_2), 4.41 (2H, 2 x t, *J* 8.0, NCH_2), 5.78 (1H, dd, *J* 5.7, 2.8, =CH *endo*), 6.15 (1H, dd, *J* 5.6, 2.9, =CH *exo*), 6.31 (1H, dd, *J* 5.6, 3.1, =CH *exo*), 6.37 (1H, dd, *J* 5.7, 3.1, =CH *endo*).

Identical to literature data.[135]

3-(3-Phenylbicylco[2.2.1]hept-5-ene-2-ylcarbonyl)-2-oxazolidinone 123c



$C_{17}H_{17}NO_3$
Mol. Wt.: 283.32

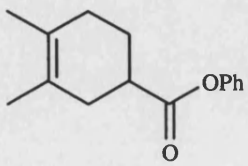
The title compound was isolated as a white solid (1.3 g, 4.6 mmol, 66%); Mp 100-103 °C; R_f (30% EtOAc/ light petroleum) 0.59; HPLC (OD column, 98:2 Hexane: propan-2-ol, 1 mL/ min) t_r = 16.2 min, 22.9 min (*exo*), 18.6 min, 34.0 min (*endo*); *endo/ exo* = 1.9:1; υ_{max} (nujol)/cm^{-1} 3068.0, 2996.3, 2929.7, 2863.2, 1767.0, 1692.0, 1492.9, 1477.7, 1454.9, 1389.6, 1333.2, 1276.9, 1214.3, 1108.4, 1078.9, 1041.1, 1025.3,

974.4, 907.0, 875.7, 850.6, 760.2, 744.8, 731.1, 698.2, 667.6; δ_H (300 MHz; $CDCl_3$) 1.48 (1H, dd, *J* 8.7, 1.1, CH *exo*), 1.58 (1H, dd, *J* 8.7, 1.5, CH *endo*), 1.84 (1H, d, *J* 8.7, CH *exo*), 1.96 (1H, d, *J* 8.7, CH *endo*), 3.00 (1H, brd s, CH *exo*), 3.11 (1H, brd d, *J* 8.6, CH), 3.35 (1H, brd d, CH *endo*), 3.47 (1H, s, CH *endo*), 3.71 (1H, d, *J* 5.1, CH *exo*), 3.89-4.05 (2H & 1H *exo*, m, CH *exo* & OCH_2); 4.19 (1H, dd, *J* 5.0, 3.4, CH *endo*), 4.30-4.43 (2H, m, NCH_2), 5.93 (1H, dd, *J* 5.5, 2.7, =CH *endo*), 6.04 (1H, dd, *J* 5.4, 2.7, =CH *exo*), 6.47 (1H, dd, *J* 5.4, 3.1, =CH *exo*), 6.53 (1H, dd, *J* 5.4, 3.2, =CH *endo*), 7.14-7.32 (5H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 43.4, 47.2 (CH2), 47.3, 47.5, 47.9 (CH), 48.6 (CH2), 49.5, 50.1, 50.5, 50.7 (CH), 62.4 (CH_2), 126.6, 128.0, 128.4, 128.9, 132.6, 136.3, 137.5, 140.6 (Ar-CH), 143.4, 144.2 (Ar-C), 153.8, 174.3, 175.0 (C=O); *m/z* (EI) 283.1 (M^+, 44%), 218.1 (96%), 165.1 (7%), 131.0 (100%), 103.0 (18%), 77.0 (10%), 66.0 (16%); (Found: M^+ 283.1212. $C_{17}H_{17}NO_3$ requires 283.1280) (Found: C, 71.0, H, 6.01, N, 4.9. $C_{17}H_{17}NO_3$ requires C, 71.6, H, 6.71, N, 4.9).

Identical to literature data.[135]

Compounds of interest that did not react under these conditions could be produced by heating the required diene and dienophile to reflux in toluene in a sealed pressure tube.

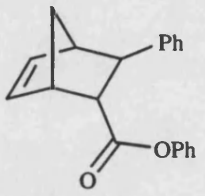
3,4-Dimethyl-cyclohex-3-enecarboxylic acid phenyl ester 118b



$C_{15}H_{18}O_2$
Mol. Wt.: 230.30

The title compound was obtained as a viscous oil (151 mg, 0.7 mmol, 66%); R_f (20% EtOAc/ light petroleum) 0.19; ν_{max} (film)/cm^{-1} 2929.7, 2852.9, 1757.0, 1588.1, 1490.8, 1444.7, 1383.2, 1296.2, 1198.9, 1157.9, 1116.9, 1065.7, 963.3, 907.0, 840.4, 732.9, 697.0; δ_H (300 MHz; $CDCl_3$) 1.64 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.72-1.86 (1H, m, CH), 2.02-2.16 (3H, m, CH & CH_2), 2.22-2.40 (2H, m, CH_2), 2.73-2.82 (1H, m, CHC=O), 7.05-7.69 (2H, m, Ar-H), 7.17-7.23 (1H, m, Ar-H), 7.33-7.39 (2H, m, Ar-H).

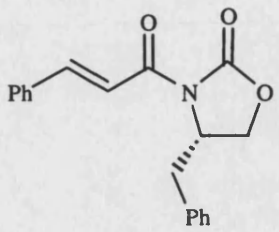
Phenyl–3-phenyl bicyclo[2.2.1]hept-5-ene-2-carboxylate 122c



$C_{20}H_{18}O_2$
Mol. Wt.: 290.36

The title compound was isolated as a colourless oil (57 mg, 0.2 mmol, 10%); R_f (20% EtOAc/ light petroleum) 0.67; ν_{max} (film)/cm^{-1} 3068.0, 3021.9, 2975.8, 1575.0, 1495.9, 1326.9, 1239.8, 1198.9, 1163.0, 1132.3, 1101.6, 973.5, 907.0, 732.9, 702.1, 686.8; δ_H (270 MHz; $CDCl_3$) 1.59-1.67 (1H, m, CH), 1.87 (1H, d, *J* 8.6, CH *exo*); 1.95 (1H, d, *J* 8.6, CH *endo*), 2.76 (1H, dd, *J* 5.2, 1.7, CH *endo*), 3.10 (1H, brd d, *J* 1.7, CH *exo*), 3.24 (1H & 1H *exo*, brd s, CH & CH *exo*), 3.32 (1H, brd s, CH *endo*), 3.46 (1H, brd s, CH *exo*), 3.83 (1H, dd, *J* 5.2, 3.5, CH *endo*), 6.07 (1H, dd, *J* 5.6, 3.0, =CH *endo*), 6.26 (1H, dd, *J*, 5.6, 2.6, =CH *exo*), 6.37 (1H, dd, *J* 5.6, 3.5, =CH *endo*), 6.48 (1H, dd, *J*, 3.0, 5.6, =CH *exo*), 7.03-7.39 (10H, m, Ar-H).

Synthesis of (*S*)-4-benzyl-oxazolidinyl (2*E*)-3-phenyl-2-propenoate 124

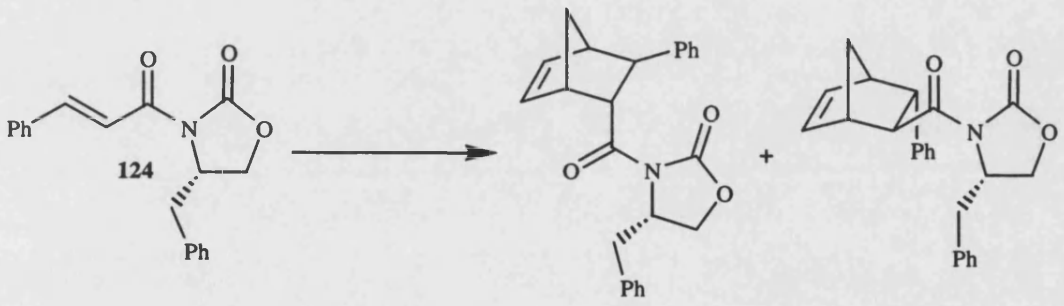


$C_{19}H_{17}NO_3$
Mol. Wt.: 307.34

n-BuLi (4 mL (2.5 M solution in hexanes), 10 mmol, 1 Eq.) was added dropwise to a stirred solution of 2-oxazolidinone (1.78 g, 10 mmol, 1 Eq.) in anhydrous THF (20 mL) at –78 °C under nitrogen. The reaction was stirred for 15 min at this temperature when a solution of cinnamoyl chloride (1.68 g, 11 mmol, 1.1 Eq.) in anhydrous THF (10 mL) was added slowly. The reaction was stirred at this temperature for 30 min and at 0 °C for a further 15 min when the reaction was quenched by addition of excess saturated ammonium chloride. The solvent was concentrated *in vacuo* to give a pale yellow oil, which was diluted with diethyl ether (50 mL). The organic layer was washed with saturated sodium bicarbonate (3 x 30 mL) and brine (2 x 30 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (10% EtOAc/ light petroleum to 35% EtOAc/ light petroleum) to give the desired product as a white solid (2.54 g, 0.83 mmol, 83%); Mp 125-127 °C; R_f (35% EtOAc/ light petroleum) 0.67; $[\alpha]_D^{25}$ +1.25° (*c*= 0.2, $CHCl_3$); HPLC (AD column, 95:5 Hexane:propan-2-ol, 1 mL/ min) t_r = 9.9 min; υ_{max} (nujol)/cm^{-1} 3062.9, 3021.9, 2955.3, 2909.3, 1777.9, 1758.8, 1673.3, 1618.2, 1577.7, 1497.9, 1474.6, 1450.3, 1392.1, 1350.2, 1287.2, 1213.3, 1122.4, 1082.9, 1063.7, 1043.1, 1013.7, 1000.7, 870.2, 835.1, 763.0, 749.4, 714.3, 693.9, 680.1, 667.0, 663.5; δ_H (400 MHz; $CDCl_3$) 2.86 (1H, dd, *J* 13.5, 9.6 , ArC*H*H), 3.38 (1H, dd, *J* 13.5, 3.3, ArCH*H*), 4.21 (1H, dd, *J* 9.0, 3.5, OC*H*H), 4.25 (1H, dd, *J* 16.8, 3.5, OCH*H*), 4.78-4.84 (1H, m,

NCH), 7.24-7.44 (8H, m, Ar-H), 7.62-7.67 (2H, m, Ar-H), 7.91 (1H, d, *J* 15.6, =CH), 7.95 (1H, d, *J* 15.6, =CH); δ_C (100.6 MHz; $CDCl_3$) 38.0 (CH_2), 55.5 (CH), 66.2 (CH_2), 116.9 (CH), 127.2, 128.6, 128.8, 128.9, 129.4, 130.6 (Ar-H), 134.4, 135.2 (Ar-C), 146.3 (=CH), 153.4 (C=O), 165.0 (C=O); *m/z* (FAB) 308.2 (M^+, 100%), 131.1 (C_9H_7O, 62%); (Found: M^+ 307.0950. $C_{19}H_{17}NO_3$ Requires 307.1208) (Found: C, 74.3, H, 5.54, N, 4.5. $C_{19}H_{17}NO_3$ requires C, 74.3, H, 5.58, N, 4.6).

Synthesis of (*S*)-4-benzyl-3-(3-phenylbicylco[2.2.1]hept-5-ene-2-ylcarbonyl]-2-oxazolidinone 125 and 126

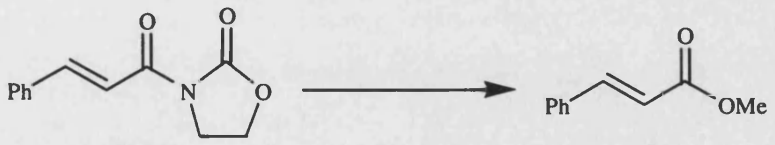


$C_{24}H_{23}NO_3$
Mol. Wt.: 373.44

Freshly prepared cyclopentadiene monomer (0.82 mL, 10 mmol, 5 Eq.) was added dropwise to a stirred solution of benzyl oxazolidinyl cinnamate **124** (0.62 g, 2 mmol, 1 Eq.) in DCM (2 mL) and ytterbium triflate (0.12 g, 0.2 mmol, 10 mol%) at room temperature under nitrogen. The solution was heated to reflux for six hours at which time the reaction was deemed to be complete as judged by TLC analysis. The solvent was removed in vacuo and the residue purified by column chromatography (10% EtOAc/ light petroleum) to yield the desired cycloadducts as separable diastereomers (0.72 g, 1.9 mmol, 95%); R_f (10% EtOAc/ light petroleum) 0.11, 0.06; HPLC (OD

column, 98:2 Hexane: propan-2-ol, 1 mL/ min) t_r = 20.9 min (*exo*), 22.8 min, 27.8 min (*endo*); *endo*/ *exo* = 1:1.4; ν_{max} (film)/cm^{-1} 3052.6, 3027.0, 2980.9, 1767.3, 1700.7, 1388.3, 1347.4, 1209.1, 1106.7, 1055.5, 1019.6, 912.1, 763.6, 732.9, 702.1; δ_H (300 MHz; $CDCl_3$) 1.49-1.63 (1H, m, CH), 1.73 (1H, brd s, CH *endo*), 1.85 (1H, brd d, CH *exo*), 1.93-1.99 (1H, m, CH), 2.66-2.89 (1H, m, CH), 3.01-3.41 (3H, m, CH & CH_2), 3.56 (1H, brd s, CH *endo*), 3.63 (1H, brd d, CH *exo*), 4.05-4.21 (3H, m, CH & CH_2), 4.58-4.67 (1H, m, CH), 5.94-5.99 (1H, m, =CH *endo*), 6.03-6.06 (1H, m, =CH *exo*), 6.47-6.50 (1H, m, =CH *exo*), 6.55-6.58 (1H, m, =CH *endo*), 7.14-7.35 (10H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 38.5, 38.6, 47.2 (CH_2), 47.3, 47.7, 47.8, 47.9 (CH), 48.0 (CH_2), 49.6, 49.7, 50.4, 50.8, 55.8, 55.9 (CH), 66.4 (CH_2), 126.6, 127.7, 127.8, 128.1, 128.5, 129.3, 129.4, 129.9, 130.0 136.3, (Ar-CH), 137.6 (Ar-C), 138.0, 139.2, 140.8, 140.9 (Ar-CH), 144.2, 145.0 (Ar-C), 153.7 (C=O), 174.4, 174.6 (C=O); *m/z* (EI) 373.1 (M^+, 37%), 308.1 (27%), 131.0 (55%), 117.1 (8%), 91.0 (16%), 66.0 (17%), 43.0 (100%) (Found: C, 76.9, H, 6.32, N, 3.7. $C_{24}H_{23}NO_3$ requires C, 76.8, H, 6.71, N, 3.7).

General procedure (13) for the methanolysis of oxazolidinyl cinnamate 123a

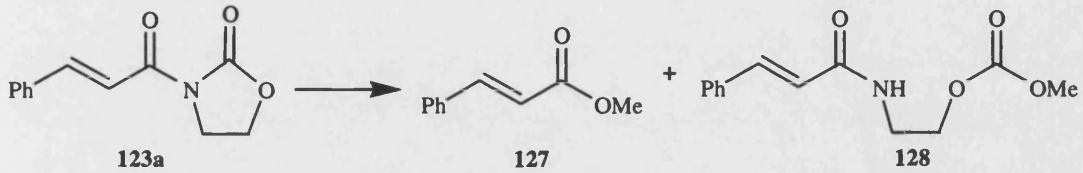


123a **127**

Anhydrous methanol (3 mL, 48 mmol, 198 Eq.) was added to a stirred solution of oxazolidinyl cinnamate (54 mg, 0.25 mmol, 1 Eq.) and the requisite catalyst (1 Eq. or 10 mol%) in anhydrous acetonitrile (2 mL). The reaction was followed by reverse phase HPLC analysis after prior calibration with known standards. Each analytical

sample was prepared by passing it through a pad of silica. The reactions were quenched with water (10 mL), extracted with diethyl ether (3 x 30 mL), dried over Na_2SO_4 and evaporated to dryness. Column chromatography (8% EtOAc/ light petroleum) allowed confirmation of the conversions obtained by HPLC analysis.

DMAP catalysed methanolysis of oxazolidinyl cinnamate 123a



123a **127** **128**

$C_{13}H_{15}NO_4$
Mol. Wt.: 249.26

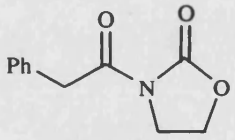
The general procedure **12** for the catalysed methanolysis of oxazolidinyl cinnamate **123a** was used. Column chromatography (10% EtOAc/ light petroleum) allowed the isolation of the desired product methyl cinnamate **127** (100 mg, 0.62 mmol, 62%) and the product of endocyclic ring cleavage, carbonic acid methyl ester 2-(3-phenyl-acryloylamino)-ethyl ester **128** as a white solid (97 mg, 0.39 mmol, 39%); Mp 96-98 °C; R_f (20% EtOAc/ light petroleum) 0.27; υ_{max} (nujol)/cm^{-1} 3308.7, 3073.1, 2986.1, 2924.6, 2863.2, 1731.4, 1654.6, 1623.9, 1557.3, 1449.8, 1347.4, 1301.3, 1285.9, 1239.8, 1229.6, 1060.6, 1035.0, 973.5, 901.9, 860.9, 799.4, 763.6, 717.5, 702.1; δ_H (300 MHz; $CDCl_3$) 3.70 (2H, q, *J* 5.2 NCH_2), 3.82 (3H, s, OMe), 4.31 (2H, t, *J* 5.2, OCH_2), 6.07 (1H, brd t, NH), 6.41 (1H, d, *J* 15.6, =CH), 7.36-7.39 (3H, m, Ar-H), 7.49-7.52 (2H, m, Ar-H), 7.65 (1H, d, *J* 15.6, =CH);); δ_C (75.5 MHz; $CDCl_3$) 38.2 (CH_2), 54.4 (OMe), 66.3 (CH_2), 119.5 (=CH), 127.2, 128.2, 129.2 (Ar-H), 134.0 (Ar-C), 141.0 (=CH), 155.0, 165.3 (C=O); *m/z* (FAB) 250.1 (M+H, 100%), 174.1 (M-

OCOOMe, 27%), 131.0 (M-$C_4H_8NO_3$, 54%); (Found: M^+ 249.1000. $C_{13}H_{15}NO_4$ requires 249.1001) (Found: C, 62.7, H, 6.04, N, 5.6. $C_{13}H_{15}NO_4$ requires C, 62.6, H, 6.07, N, 5.6).

Preparation of other *N*-acyl oxazolidinyl substrates

Other N-acyl oxazolidinyl substrates were prepared from the requisite acid chlorides in an analogous manner to oxazolidinyl (2*E*)-3-phenyl-2-propenoate **123a**.

3-Phenylacetyl-2-oxazolidinone

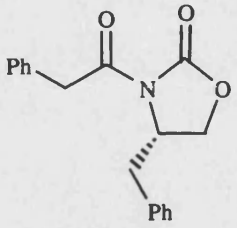


$C_{11}H_{11}NO_3$
Mol. Wt.: 205.21

The title compound was isolated as a white solid (5.75 g, 28 mmol, 56%); Mp 69-71 °C (lit.[137] 66-67 °C); R_f (33% EtOAc/ light petroleum) 0.10; υ_{max} (nujol)/cm^{-1} 3021.9, 2988.6, 2912.7, 1763.4, 1688.3, 1481.4, 1456.3, 1397.8, 1379.3, 1274.1, 1250.9, 1222.5, 1202.7, 1120.3, 1034.0, 1018.3, 1003.3, 963.6, 759.9, 740.6, 703.9, 679.2; δ_H (300 MHz; $CDCl_3$) 4.01 (2H, t, *J* 8.1, OCH_2), 4.28 (2H, s, $PhCH_2$), 4.38 (2H, t, *J* 8.1, NCH_2), 7.26-7.33 (5H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 41.5, 43.1, 62.4 (CH_2), 127.6, 128.9, 130.1 (Ar-CH), 133.9 (Ar-C), 153.9, 171.7 (C=O); *m/z* (EI) 205.0 (M^+, 25%), 118.0 (M-$C_3H_5NO_2$, 100%), 91.0 (M-$C_4H_4NO_3$, 41%), 65.0 (C_5H_5, 10%); (Found M^+ 205.0734. $C_{11}H_{11}NO_3$ requires 205.0739).

Identical to literature data.[137]

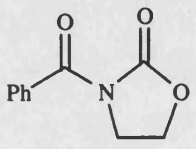
(*S*)-4-Benzyl-3-phenylacetyl-2-oxazolidinone



$C_{18}H_{17}NO_3$
Mol. Wt.: 295.33

The title compound was isolated as a white solid (1.6 g, 5.3 mmol, 75%). Mp 66-68 °C; R_f (20% EtOAc/ light petroleum) 0.22; υ_{max} (nujol)/cm^{-1} 3027.0, 2980.9, 2929.7, 1767.3, 1711.0, 1593.2, 1449.8, 1383.2, 1357.6, 1209.1, 1106.7, 1035.0, 994.0, 840.4, 763.6, 722.6, 697.0; δ_H (300 MHz; $CDCl_3$) 2.76 (1H, dd, *J* 13.4, 9.5, ArC*H*HCN), 3.28 (1H, dd, *J* 13.4, 3.3, ArCH*H*CN), 4.16-4.21 (2H, m, OCH_2), 4.27 (1H, d, *J* 15.8, ArC*H*HCO), 4.35 (1H, d, *J* 15.8, ArCH*H*CO), 4.64-4.72 (1H, m, NCH); δ_C (75.5 MHz; $CDCl_3$) 38.1 (Ar*C*H_2CO), 42.0 (OCH_2), 55.7 (NCH), 66.5 (Ar*C*H_2CHN), 127.6, 127.7, 129.0, 129.4, 129.8, 130.2 (Ar-CH), 133.9, 135.5 (Ar-C), 153.8, 171.6 (C=O).

3-Benzoyl-2-oxazolidinone

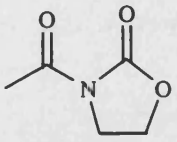


$C_{10}H_9NO_3$
Mol. Wt.: 191.18

Title compound was obtained as a white solid (6.0 g, 32 mmol, 63%); Mp 159-161 °C (lit.[138] 167-167.5 °C); R_f (20% EtOAc/ light petroleum) 0.06; υ_{max} (nujol)/cm^{-1} 2981.8, 2914.4, 1813.4, 1773.9, 1721.1, 1675.5, 1467.1, 1447.5, 1379.0, 1357.4, 1336.5, 1272.7, 1238.4, 1211.6, 1200.9, 1184.5, 1107.2, 1080.3, 1038.5, 989.7, 932.2, 911.3, 866.7, 794.7, 757.2, 750.2, 718.4, 698.2, 662.9; δ_H (300 MHz; $CDCl_3$) 4.18 (2H, t, *J* 7.7 OCH_2), 4.50 (2H, t, *J* 7.7, NCH_2), 7,41-7.46 (2H, m, Ar-H), 7.53-7.55 (1H, m, Ar-H), 7.65-7.68 (2H, m, Ar-H); δ_c (75.5 MHz; $CDCl_3$) 44.1 (CH_2), 62.6 (CH_2), 128.3, 129.5, 132.8 (Ar-CH), 133.0 (Ar-C), 153.6 (C=O), 170.2 (C=O); *m/z* (EI) 191.0 (M^+, 38%), 132.0 (M-$HNCO_2$, 100%), 105.0 (M-$C_3H_4NO_2$, 40%), 70.0 (43%), 57.0 (28%), 41.0 (32%), 29.0 (25%); (Found: M^+ 191.0578 $C_{10}H_9NO_3$ Requires 191.0582).

Identical to literature data.[138]

3-Acetyl-2-oxazolidinone



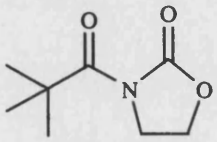
$C_5H_7NO_3$
Mol. Wt.: 129.11

The title compound was isolated as a colourless solid (4.6 g, 36 mmol, 72%) Mp 62-64 °C (lit.[138] 63-64 °C); R_f (50% EtOAc/ light petroleum) 0.33; υ_{max} (nujol)/cm^{-1} 2992.0, 2912.7, 1768.4, 1692.6, 1474.7, 1390.2, 1376.3, 1310.2, 1224.8, 1142.4, 1122.6, 1062.7, 1041.4, 991.0, 959.3, 759.5, 717.1, 679.2, 668.0; δ_H (300 MHz; $CDCl_3$) 2.53 (3H, s, CH+), 4.03 (2H, t, *J* 8.1, OCH_2), 4.42 (2H, t, *J* 8.1, NCH_2); δ_C

(75.5 MHz; $CDCl_3$) 23.3 (CH_3), 42.4, 62.0 (CH_2), 153.7 (C=O), 170.5 (C=O); m/z (EI) 129.0 (M^+, 29%), 101.0 (M-CO, 45%), 88.0 (M-CO_2H, 21%), 57.0 (M-$(CH_2)_2CO_2$, 6%), 43.0 (CH_3O, 100%), 28.0 (CO, 7%); (Found M^+ 129.0420. $C_5H_7NO_3$ requires 129.0426).

Identical to literature data.[138]

3-(2,2-Dimethyl-propionyl)-2-oxazolidinone

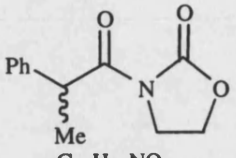


$C_8H_{13}NO_3$
Mol. Wt.: 171.19

Title compound was obtained as a colourless oil (4.5 g, 26 mmol, 52%); R_f (20% EtOAc/ light petroleum) 0.21; υ_{max} (film)/cm^{-1} 2970.7, 2924.6, 2868.3, 1777.5, 1690.5, 1485.6, 1383.2, 1362.7, 1291.0, 1188.6, 1111.8, 1040.1, 994.0, 947.9, 748.2, 722.6; δ_H (300 MHz; $CDCl_3$) 1.38 (9H, s, ^tBu), 4.05 (2H, t, *J* 8.1, OCH_2), 4.40 (2H, t, *J* 8.1, NCH_2); δ_c (75.5 MHz; $CDCl_3$) 26.3 (CH_3), 41.4, 45.2 (CH_2), 62.2 (CH_2), 152.4 (C=O), 178.8 (C=O).

Identical to literature data.[139]

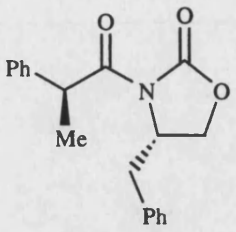
3-(2-Phenyl-propionyl)-2-oxazolidinone



$C_{12}H_{13}NO_3$
Mol. Wt.: 219.24

n-BuLi (3.1 mL (1.5 M in hexanes), 7.7 mmol, 1.1 Eq.) was added to a stirred solution of diisoproylamine (1.2 mL, 8. 47 mmol, 1.21 Eq.) in anhydrous THF (30 mL) at 0 °C under nitrogen. The reaction was left at this temperature for 20 minutes, when it was cooled to –78 °C. A solution of 3-phenylacetyl-2-oxazolidinone (1.4 g, 7 mmol, 1 Eq.) in anhydrous THF (5 mL) was added to the resultant solution of LDA. The reaction was stirred at this temperature for 15 minutes when it was warmed to room temperature. Methyl iodide (1.3 mL, 21 mmol, 3 Eq.) was added to this suspension and the reaction was stirred at 0 °C for 3 hours. The reaction was quenched by adding excess saturated aqueous ammonium chloride solution. The solvents were removed *in vacuo* and the resultant oil diluted with DCM, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (33 % EtOAc/ light petroleum) to give a colourless viscous oil (1.1 g, 5.1 mmol, 73 %); HPLC (OD column, 95:5 Hexane:propan-2-ol, 1 mL/ min) t_r = 27.2, 33.8; δ_H (300 MHz; $CDCl_3$) 1.50 (3H, d, *J* 7.0, CH_3), 3.88-4.10 (2H, m, OCH_2), 4.24-4.41 (2H, m, NCH_2), 5.10 (1H, q, *J* 7.0, CH), 7.24-7.38 (5H, m, Ar-H); *m/z* (EI) 219.1 (M^+, 23%), 132.1 (M- $C_3H_5NO_2$, 100%), 105.1 (M- $C_4H_4NO_3$, 78%), 77.0 (37%), 51.0 (18%), 42.0 (11%), 26.7 (12%); (Found M^+ 219.0888. $C_{12}H_{13}NO_3$ requires 219.0845).

(*S*)-4-Benzyl-3-(2-phenyl-propionyl)-2-oxazolidinone



$C_{19}H_{19}NO_3$
Mol. Wt.: 309.36

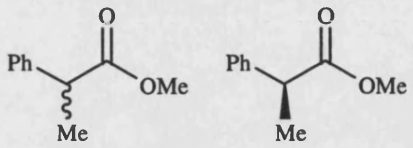
The title compound was prepared in a similar manner to 3-(2-Phenyl-propionyl)-2-oxazolidinone and isolated *via* column chromatography (10% EtOAc/ light petroleum) to give the desired product as a white solid. Mp 76-78 °C; δ_H (300 MHz; $CDCl_3$) 1.55 (3H, d, *J* 7.0, CH_3), 2.80 (1H, dd, *J* 9.8, 13.3, ArC*H*H), 3.36 (1H, dd, *J* 3.2, 13.3, ArCH*H*), 4.02-4.13 (2H, m, OCH_2), 4.56-4.62 (1H, m, NCH), 5.12 (1H, q, *J* 7.0, CH), 7.23-7.36 (10H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 19.4 (CH_3), 37.9 (Ph*C*H_2), 43.1 (NCH), 55.8 (CH), 65.9 (OCH_2), 127.3, 127.4, 128.1, 128.6, 129.0, 129.4 (Ar-CH), 135.3, 140.2 (Ar-C), 152.9, 174.6 (C=O); *m/z* (EI) 309.1 (M^+, 22%), 132.0 (M-$C_{10}H_{11}NO_2$, 87%), 105.1 (100%), 91.0 (36%), 77.0 (30%), 43.0 (19%); (Found M^+ 309.1349. $C_{19}H_{19}NO_3$ requires 309.1365) (Found: C, 73.3, H, 6.21, N, 4.52. $C_{19}H_{19}NO_3$ requires: C, 73.7, H, 6.19, N, 4.53) (Found: C, 73.9, H, 6.16, N, 4.5. $C_{19}H_{19}NO_3$ requires C, 73.8, H, 6.19, N, 4.5).

Methanolysis of other *N*-acyl oxazolidinones

Anhydrous methanol (30 mL, 0.50 mol, 198 Eq.) was added to a stirred solution of the requisite oxazolidinyl substrate (2.5 mmol, 1 Eq.) and $Yb(OTf)_3$ (0.16 g, 0.25 mmol, 10 mol%) in anhydrous acetonitrile (20 mL) at room temperature under nitrogen. The

reaction was stirred at this temperature for 17 hours when the solvent was removed *in vacuo*. Column chromatography allowed the isolation of the desired methyl ester.

Methyl-2-phenylpropenoate

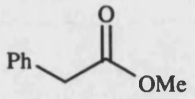


$C_{10}H_{12}O_2$
Mol. Wt.: 164.20

Title product was obtained as a colourless oil (378 mg, 2.3 mmol, 92%); R_f (10% EtOAc/ light petroleum) 0.58; HPLC (OJ column, 98:2 Hexane:Propan-2-ol, 1mL/ min): t_r = 9.1, 10.6 min (99% e.e.); υ_{max} (film)/cm^{-1} 3032.2, 2980.9, 2934.9, 1741.7, 1603.4, 1501.0, 1460.0, 1429.3, 1378.1, 1326.9, 1209.1, 1168.1, 1065.7, 1040.1, 1014.5, 855.8, 763.6, 732.9, 702.1; δ_H (300 MHz; $CDCl_3$) 1.50 (3H, d, *J* 7.2, CH_3), 3.65 (4H, s, OCH_3), 3.70 (1H, q, *J* 7.2, CH), 7.24-7.32 (5H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 18.6 (CH_3), 45.4 (CH), 52.0 (OCH_3), 127.1, 127.5, 128.6, (Ar-H), 140.6 (Ar-C), 175.0 (C=O); *m/z* (EI) 164.1 (M^+, 20%), 105.0 (M-CO_2Me, 100%), 77.0 (C_6H_5, 17%), 51.0 (C_4H_3, 9%); (Found M^+ 164.0832. $C_{10}H_{12}O_2$ requires 164.0837).

Identical to literature data.[140]

Methylphenylacetate

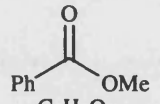


$C_9H_{10}O_2$
Mol. Wt.: 150.17

The title product was obtained as a colourless oil (347 mg, 2.3 mmol, 93%); Rf (33% EtOAc/ light petroleum) 0.52; υ_{max} (film)/cm^{-1} 3021.9, 2960.5, 2904.1, 1731.4, 1608.5, 1501.0, 1465.2, 1439.5, 1347.4, 1306.4, 1260.3, 1229.6, 1163.0, 1055.5, 1004.3, 850.6, 763.6, 727.8, 697.0; δ_H (300 MHz; $CDCl_3$) 3.60 (2H, s, CH_2), 3.65 (3H, s, OCH_3), 7.20-7.34 (5H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 41.2 (CH_2), 52.0 (OCH_3), 127.1, 128.8, 129.3 (Ar-CH), 134.0 (Ar-C), 172.0 (C=O).

Identical to literature data.[141]

Methylbenzoate

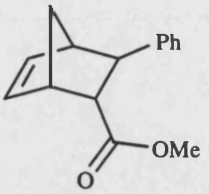


$C_8H_8O_2$
Mol. Wt.: 136.15

Title product was isolated as a colourless oil (252 mg, 1.9 mmol, 74%); R_f (20% EtOAc/ light petroleum) 0.63; υ_{max} (film)/cm^{-1} 3078.2, 2950.2, 2842.7, 1721.2, 1598.3, 1460.0, 1439.5, 1306.4, 1275.7, 1198.9, 1173.3, 1111.8, 1070.8, 1035.0, 968.4, 830.2, 702.1;

Identical to literature data.[142]

Methyl–3-phenyl bicyclo[2.2.1]hept-5-ene-2-carboxylate



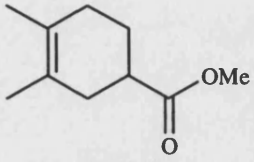
$C_{15}H_{16}O_2$
Mol. Wt.: 228.29

The title compound was isolated as a colourless oil (569 mg, 2.49 mmol, 99%); R_f (33% EtOAc/ light petroleum) 0.71; GC (β-dex column, 140 °C) t_r = 172.3 min, 173.1 min (*endo*), 174.3, 177.3 (*exo*); *endo*:*exo* = 1.7:1; υ_{max} (film)/cm^{-1} 2990.2, 2945.1, 1736.6, 1598.3, 1495.9, 1429.3, 1332.0, 1270.6, 1204.0, 1168.1, 1111.8, 1060.6, 1029.9, 912.1, 860.9, 722.6, 691.9; δ_H (300 MHz; $CDCl_3$) 1.54-1.58 (1H, m, CH), 1.77 (1H, d, *J* 8.7, CH *endo*), 1.88 (1H, d, *J* 8.6, CH *exo*), 2.51 (1H, m, CH *exo*), 2.98 (2H *exo* & 1H *endo*, m, CH *endo* & CH_2 *exo*), 3.12 (2H *endo* & 1H *exo*, m, CH *exo* & CH_2 *endo*), 3.28 (1H, brd s, CH *endo*), 3.66 (3H, s, OCH_3 *endo*), 3.70 (3H, s, OCH_3 *exo*), 6.01 (1H, dd, *J* 5.6, 2.8, =CH *exo*), 6.11 (1H, dd, *J* 5.6, 2.7, =CH *endo*), 6.30 (1H, dd, *J* 5.6, 3.2, =CH *exo*), 6.41 (1H, dd, *J* 5.6, 3.2, =CH *endo*), 7.15-7.31 (5H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 46.3 (CH), 47.2 (CH_2), 47.5 (CH), 48.0 (CH_2), 48.1, 48.3, 48.4, 48.7, 50.4 (CH), 51.7, 52.0 (OMe), 126.0, 126.2, 127.5, 127.8, 128.0, 128.5, 134.5, 135.9, 136.6, 139.1 (Ar-CH), 143.0, 144.2 (Ar-C), 174.8, 176.0 (C=O); *m/z* (EI) 222.8 (M^+, 21%), 163.1 (93%), 131.0 (82%), 115.0 (10%), 103.0 (24%), 91.0 (15%), 77.0 (16%), 66.0 (100%), 38.9 (12%); (Found: M^+ 228.1149. $C_{15}H_{16}O_2$ Requires 228.1150).

Identical to literature data.[143]

Cleavage of the chiral cycloadduct **125/126** gave the title compound as a colourless oil (183 mg, 0.80 mmol, 82%). Analysis of GC and ^{1}H NMR data suggests an *endo*:*exo* ratio of 1:2. Auxiliary **130** can also be recovered (137 mg, 0.77 mol, 79%).

3,4-Dimethyl-cyclohex-3-enecarboxylic acid methyl ester

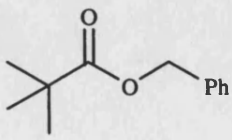


$C_{10}H_{16}O_2$
Mol. Wt.: 168.23

The title compound was isolated as a colourless glass (265 mg, 1.58 mmol, 63%); R_f (20% EtOAc/ light petroleum) 0.20; δ_H (300 MHz; $CDCl_3$) 1.57-1.71 (7H, m, CH & CH_3), 1.93-2.09 (3H, m, CH & CH_2), 2.12-2.26 (2H, m, CH_2), 2.48-2.58 (1H, m, CH), 3.68 (3H, s, OCH_3); δ_C (75.5 MHz; $CDCl_3$) 18.8, 19.0 (CH_3), 25.9, 31.0, 33.8 (CH_2), 40.2 (CH), 51.6 (OCH_3), 127.1, 128.8, 129.3 (Ar-CH), 134.0 (Ar-C), 172.0 (C=O).

Identical to literature data.[63]

Synthesis of benzyl-2,3-dimethyl propenoate

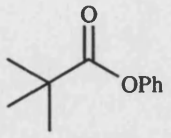


$C_{12}H_{16}O_2$
Mol. Wt.: 192.25

Pivaloyl chloride (1.9 mL, 15 mmol, 1 Eq.) was added dropwise to a stirred solution of benzyl alcohol (1.6 mL, 15 mmol, 1 Eq.), triethylamine (4.2 mL, 30 mmol, 2 Eq.) and catalytic DMAP in anhydrous DCM (25 mL) under nitrogen at 0 °C. The reaction was stirred for 3 hours when it was poured into water (30 mL) and extracted with DCM (2 x 30 mL). The combined organic extracts were washed with 2M NaOH (2 x 40 mL) and 2M HCl (1 x 40 mL), dried over $MgSO_4$ and evaporated to dryness. The crude residue was purified by column chromatography (10% EtOAc/ light petroleum) to give the desired product as a colourless oil (2.7 g, 14 mmol, 94%); R_f (10% EtOAc/ light petroleum) 0.54; υ_{max} (film)/cm^{-1} 2960.5, 2899.0, 2878.5, 1736.6, 1480.5, 1460.0, 1403.7, 1357.6, 1275.7, 1142.5, 1029.9, 968.4, 860.9, 738.0, 686.8; δ_H (300 MHz; $CDCl_3$) 1.23 (9H, s, ^tBu), 5.10 (2H, s, CH_2), 7.27-7.38 (5H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 27.2 (C), 38.8 (^tBu), 66.0 (CH_2), 128.0, 128.3, 128.5 (Ar-CH), 136.5 (Ar-C), 178.3 (C=O).

Identical to literature data.[144]

Synthesis of phenyl-2,3-dimethyl propenoate



$C_{11}H_{14}O_2$
Mol. Wt.: 178.23

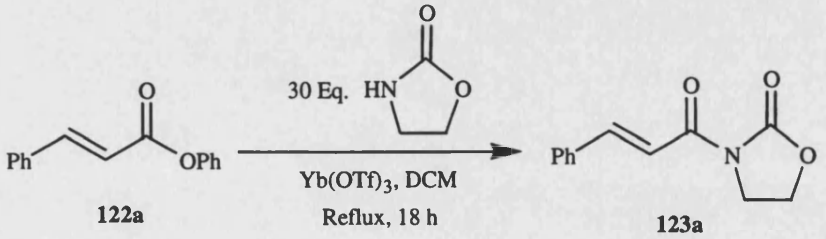
The title compound was prepared in an analogous manner as the benzyl analogue. Column chromatography (10% EtOAc/ light petroleum) allowed isolation of the desired product as a colourless oil (2.7 g, 15 mmol, 100%); R_f (10 % EtOAc/ light

petroleum) 0.51; υ_{max} (film)/cm^{-1} 2970.7, 2929.7, 2883.9, 1746.8, 1593.2, 1495.9, 1480.5, 1460.0, 1408.8, 1373.0, 1285.9, 1204.0, 1163.0, 1106.7, 1070.8, 1029.9, 922.3, 835.3, 799.4, 743.1, 681.7; δ_H (300 MHz; $CDCl_3$) 1.35 (9H, s, ^{t}Bu), 7.03-7.06 (2H, m, Ar-H), 7.20-7.22 (1H, m, Ar-H), 7.33-7.38 (2H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 27.1 (^{t}Bu), 39.0 (C), 121.5, 125.6, 129.3 (Ar-CH), 151.1 (Ar-C), 177.0 (C=O). Identical to literature data.[145]

General procedure (14) for the cleavage of *N*-acyl oxazolidinyl substrates with either phenol or benzyl alcohol

The requisite alcohol (10 mmol, 10 Eq.) was added to a stirred solution of the desired *N*-acyl oxazolidinyl substrate (1 mmol, 1 Eq.) and $Yb(OTf)_3$ (62 mg, 0.1 mmol, 1 Eq.) in anhydrous acetonitrile (5 mL) at room temperature under nitrogen. Aliquots were taken at regular intervals, quenched by passing through a small pad of silica and analysed by GC relative to an internal standard (dodecane).

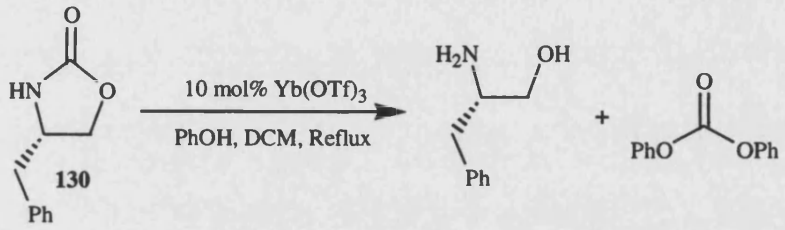
General procedure (15) for the Lewis acid catalysed formation of oxazolidinyl cinnamate 123a from cinnamyl esters



122a **123a**

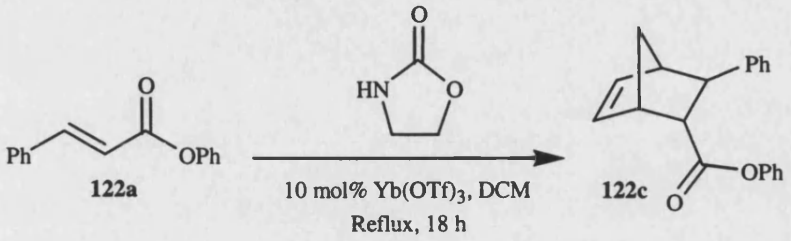
2-Oxazolidinone (0.65 g, 7.5 mmol, 30 Eq.) was added to a stirred solution of phenyl cinnamate **122a** (56 mg, 0.25 mmol, 1 Eq.) and $Yb(OTf)_3$ (16 mg, 0.025 mmol, 10 mol%) in anhydrous DCM (5 mL) at reflux under nitrogen. The reaction was stirred overnight and the solvent removed *in vacuo*. Column chromatography (33% EtOAc/ light petroleum to 50% EtOAc/ light petroleum) allowed isolation of oxazolidinyl cinnamate **123a** (6 mg, 0.025 mmol, 10%) as a white solid.

Stability of (*S*)-benzyl-2-oxazolidinone under transesterification conditions



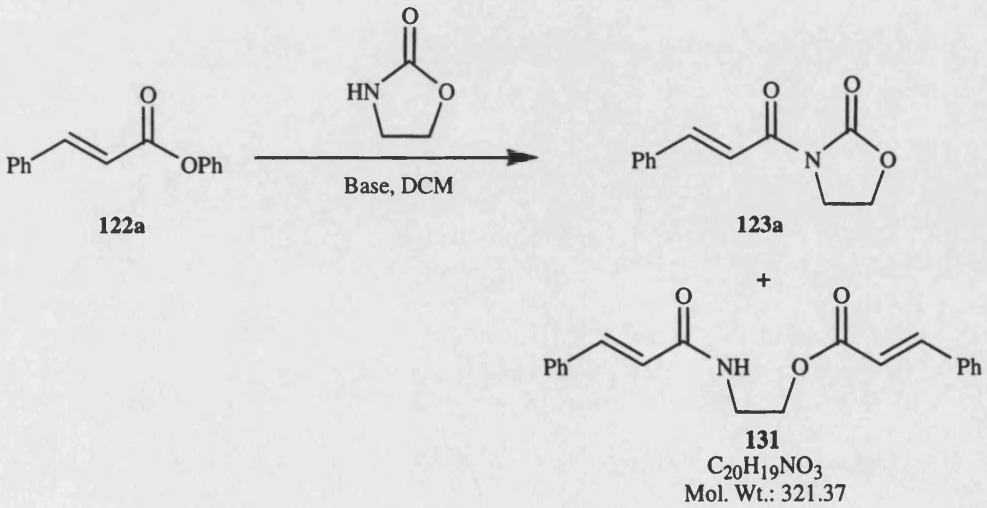
Phenol (0.24 g, 0.25 mmol, 10 Eq.) was added to a stirred solution of (S)-benzyl oxazolidinone 130 (44 mg, 0.25 mmol, 1 Eq.) and $Yb(OTf)_3$ (16 mg, 2.5×10^{-5} mol, 10 mol%) in anhydrous DCM (5 mL). The reaction was stirred at reflux overnight under nitrogen after which time the reaction was allowed to cool, quenched by passing through a pad of silica and the solvent removed *in vacuo*. ^1H NMR analysis showed no reaction had occurred, as only starting materials were present.

Attempted full cycle utilising $Yb(OTf)_3$ mediated oxazolidinyl formation as the key step



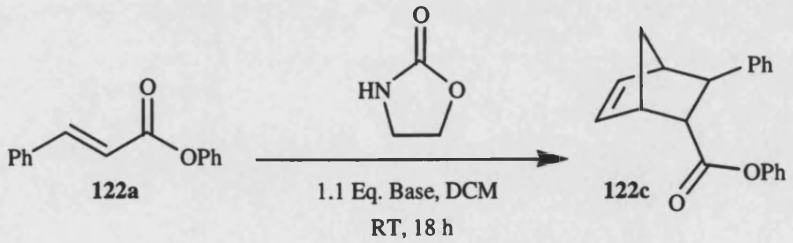
Freshly prepared cyclopentadiene monomer (0.21 mL, 2.5 mmol, 5 Eq.) was added to a stirred solution of 2-oxazolidinone (44 mg, 0.5 mmol, 1 Eq.) phenyl cinnamate **122a** (112 mg, 0.5 mmol, 1 Eq.) and $Yb(OTf)_3$ (31 mg, 0.05 mmol, 10 mol%) in anhydrous DCM (10 mL) at reflux under nitrogen every 2 hours for 10 hours. The reaction was stirred overnight and the solvent removed *in vacuo*. Column chromatography (2% Et_2O/ light petroleum to 5% Et_2O/ light petroleum) allowed isolation of the desired product **122c** (18 mg, 0.055 mmol, 11%).

General procedure (16) for the formation of oxazolidinyl cinnamate 123a from phenyl cinnamate 122a utilising deprotonated oxazolidinone



The desired base (1.1 Eq.) was added to a stirred solution of 2-oxazolidinone (87 mg, 1 mmol, 1 Eq.) in anhydrous DCM (10 mL) under nitrogen at 0 °C. The reaction was stirred for 30 minutes at this temperature and allowed to warm to room temperature for a further 30 minutes. A solution of phenyl cinnamate **122a** (0.22 g, 1 mmol, 1 Eq.) in anhydrous DCM (10 mL) was added *via* syringe and the reaction left for 18 hours. Column chromatography (10 % EtOAc/ light petroleum to 33% EtOAc/ light petroleum) allowed isolation of oxazolidinyl cinnamate **123a** and the dimeric impurity **131** (23 mg, 0.07 mmol, 7% from 15% SM); R_f (33% EtOAc/ light petroleum) 0.15; δ_H (300 MHz; $CDCl_3$) 3.75 (1H, dt, *J* 5.5, 5.2, NCH_2), 4.39 (2H, t, *J* 5.2, OCH_2), 6.09 (1H, brd s, NH), 6.42 (1H, d, *J* 15.6, =CH), 6.48 (1H, d, *J* 16.0, =CH), 7.35-7.41 (6H, m, Ph-H), 7.49-7.56 (4H, m, Ph-H), 7.66 (1H, d, *J* 15.6, =CH), 7.74 (1H, d, *J* 16.0, =CH); *m/z* (FAB) 322.2 (M^+, 47%), 274.2 (M-CH_3O, 6%), 243.2 (M-C_6H_6, 6%), 217.1 (M-C_8H_8, 9%), 179.2 (M-C_9H_9NO, 13%), 131.1 (M-$C_{11}H_{12}NO_2$, 61%), 111.2 (53%), 97.1 (100%), 82.1 (17%), 68.1 (20%); (Found: MH^+ 322.1436. $C_{20}H_{20}NO_3$ requires 322.1443).

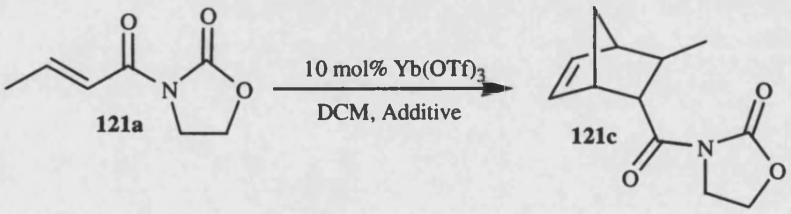
Attempted full cycle utilising deprotonated oxazolidinone



The requisite base (1.1 Eq.) was added to a stirred solution of 2-oxazolidinone (87 mg, 1 mmol, 1 Eq.) in anhydrous DCM (10 mL) at 0 °C under nitrogen. The reaction was

stirred at this temperature for 30 minutes and allowed to warm to room temperature for a further 30 minutes. A solution of phenyl cinnamate **122a** (0.22 g, 1 mmol, 1 Eq.) in anhydrous DCM was added *via* syringe followed by the desired Lewis acid catalyst (10 mol%) and freshly prepared cyclopentadiene (0.82 mL, 10 mmol, 10 Eq.) The reaction was stirred overnight. The crude reaction mixture was washed with 2M NaOH (2 x 20 mL), 2M HCl (2 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography allowed isolation of all products and intermediates. This reaction was also run utilising other dienophile/ diene systems.

Effect of various additives on the reaction between oxazolidinyl crotonate 121a and cyclopentadiene

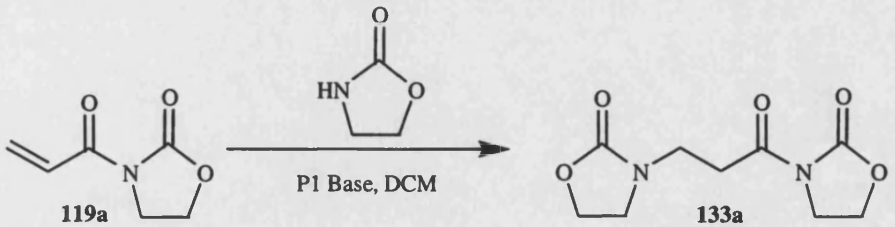


121a **121c**

$Yb(OTf)_3$ (62 mg, 0.1 mmol, 10 mol%) was added to a stirred solution of the desired additive (1 Eq. 2-oxazolidinone, 1.01 Eq. Et_3N or both) in anhydrous DCM (5 mL) at room temperature under nitrogen. After stirring for 10 minutes at this temperature oxazolidinyl crotonate **121a** (0.16 g, 1 mmol, 1 Eq.) and freshly prepared cyclopentadiene monomer (0.4 mL, 5 mmol, 5 Eq.) were added and the reaction was allowed to stir for 18 hours. The reaction was quenched by addition of water (5 mL) and the phases separated. The aqueous layer was washed with DCM (3 x 5 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Column

chromatography (33% EtOAc/ light petroleum) gave the desired product **121c** as a white solid.

Synthesis of 3-(3-(2-Oxo-oxazolidin-3-yl)-propionyl)-2-oxazolidinone 133a



119a

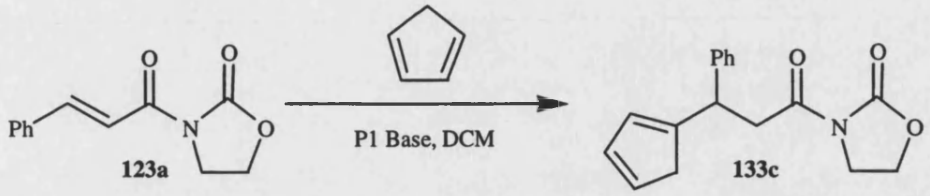
133a

$C_9H_{12}N_2O_5$

Mol. Wt.: 228.20

Phosphazene base P1-t-Bu-tris(tetramethylene) 133 (0.3 mL, 1 mmol, 1 Eq.) was added to a stirred solution of 2-oxazolidinone (89 mg, 1 mmol, 1 Eq.) and oxazolidinyl acrylate (0.14 g, 1 mmol, 1 Eq.) in anhydrous DCM (5 mL) under nitrogen at room temperature. The reaction was stirred at this temperature for 18 hours. The reaction was quenched by addition of 1M HCl (10 mL) and the aqueous layer washed with DCM (3 x 5 mL), dried over $MgSO_4$ and evaporated to dryness. Column chromatography (100% EtOAc) allowed isolation of the title compound as a white solid (61 mg, 0.27 mmol, 27%); Mp 150-152 °C; R_f (50% EtOAc/ light petroleum) 0.42; ν_{max} (nujol)/cm^{-1} 2991.2, 2970.7, 2919.5, 1762.2, 1675.1, 1618.8, 1470.3, 1403.7, 1357.6, 1239.8, 1209.1, 1111.8, 1035.0, 773.8, 753.3, 712.4; δ_H (300 MHz; $CDCl_3$) 3.23 (2H, t, *J* 6.6, CH_2), 3.62-3.69 (4H, m, CH_2), 4.02 (2H, t, *J* 8.0, CH_2), 4.32 (2H, t, *J* 8.0, CH_2), 4.45 (2H, t, *J* 8.0, CH_2); δ_C (75.5 MHz; $CDCl_3$) 33.62 (CH2), 39.76 (CH2), 43.46 (CH2), 45.02 (CH2), 61.92 (CH2), 62.32 (CH2), 153.60 (C=O), 158.43 (C=O), 171.03 (C=O).

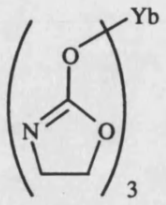
Synthesis of 3-(3-Cyclopenta-1,3-dienyl-3-phenyl-propinyl)-2-oxazolidinone 133c



$C_{17}H_{17}NO_3$
Mol. Wt.: 283.32

Phosphazene base P1-t-Bu-tris(tetramethylene) **133** (0.3 mL, 1 mmol, 1 Eq.) was added to a stirred solution of freshly prepared cyclopentadiene monomer (0.4 mL, 5 mmol, 5 Eq.) and oxazolidinyl cinnamate (0.22 g, 1 mmol, 1 Eq.) in anhydrous DCM (5 mL) under nitrogen at room temperature. The reaction was stirred at this temperature for 18 hours. The reaction was quenched by addition of 1M HCl (10 mL) and the aqueous layer washed with DCM (3 x 5 mL), dried over $MgSO_4$ and evaporated to dryness. Column chromatography (100% EtOAc) allowed isolation of the title compound as a white solid (61 mg, 0.22 mmol, 22%); R_f (100% EtOAc) 0.13; δ_H (300 MHz; $CDCl_3$) 2.82-2.83 (1H, m, CH), 2.98-2.99 (1H, m, CH), 3.60 (2H, d, *J* 7.5, CH_2), 3.85-3.99 (2H, m, OCH_2), 4.27-4.43 (3H, m, NCH_2 & CH), 6.14-6.42 (3H, m =CH), 7.16-7.31 (5H, m Ar-H); δ_C (75.5 MHz; $CDCl_3$) 40.27, 40.63, 41.22, 41.79, 42.51, 42.61, 42.69, 61.99, 126.19, 126.52, 126.57, 126.88, 127.82, 128.08, 128.44, 128.47, 131.85, 131.93, 133.84, 134.12, 142.70, 143.55, 148.58, 150.78, 153.51, 171.64, 171.69.

Synthesis of $Yb(Ox)_3$

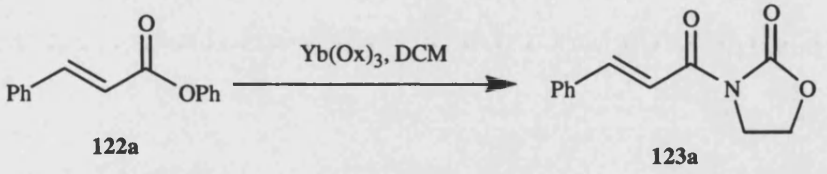


134

$C_9H_{12}N_3O_6Yb$
Mol. Wt.: 431.25

2-Oxazolidinone (0.13 g, 1.5 mmol, 3 Eq.) was added portionwise to a stirred suspension of sodium hydride (66 mg, (60% w/w in mineral oil), 1. 65 mmol, 3.3 Eq.) in anhydrous DCM (5 mL) under nitrogen at room temperature. The reaction was stirred for 15 minutes and $Yb(OTf)_3$ (0.31 g, 0.5 mmol, 1 Eq.) was added. The reaction was stirred for four hours at which time the title compound was collected as a white solid, by filtration.

Attempted formation of oxazolidinyl cinnamate utilising $Yb(Ox)_3$ as a catalyst



122a **123a**

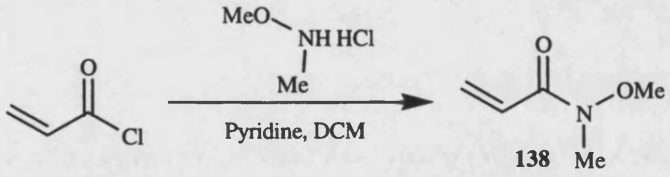
Phenyl cinnamate **122a** (0.22 g, 1 mmol, 1 Eq.) was added to a stirred suspension of $Yb(Ox)_3$ (129 mg, 0.33 mmol, 1 Eq. oxazolidinone) in anhydrous DCM (5 mL) at room temperature under nitrogen. The reaction was stirred at this temperature for 72 hours at which time none of the desired product was visible as determined by TLC and ^1H NMR analysis of the crude reaction mixture.

Attempted formation of 3-(3-phenylbicylco[2.2.1]hept-5-ene-2-ylcarbonyl)-2-oxazolidinone 123c utilising $Yb(Ox)_3$ as a catalyst

Freshly prepared cyclopentadiene monomer (0.4 mL, 5 mmol, 5 Eq.) was added to a stirred solution of oxazolidinyl cinnamate **123a** (0.22 g, 1 mmol, 1 Eq.) and $Yb(Ox)_3$ (43 mg, 0.1 mmol, 10 mol%) in anhydrous DCM at room temperature under nitrogen. The reaction was stirred for 48 hours and was quenched with 1M HCl (5 mL). The aqueous layer was extracted with DCM (2 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Analysis of the ^1H NMR of the crude reaction mixture showed the title product to be formed in 8% conversion.

5.4 Experimental for Chapter 4

Synthesis of *N*-Methoxy-*N*-methylacrylamide 138



138

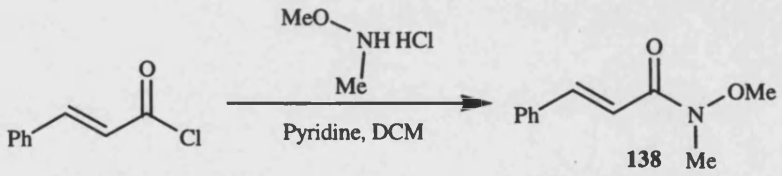
$C_5H_9NO_2$
Mol. Wt.: 115.13

Anhydrous pyridine (8.9 mL, 110 mmol, 2.2 Eq.) was added slowly to a stirred slurry of N,O-methyl methoxylamine hydrochloride (5.1 g, 52 mmol, 1.04 Eq.) and acryloyl chloride (4.1 mL, 50 mmol, 1 Eq.) in anhydrous DCM (70 mL) at 0 °C under nitrogen. The reaction was stirred at this temperature for 15 minutes then allowed to warm to room temperature for 2 hours. The reaction was quenched by adding 5% aqueous HCl (20 mL) and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with sodium bicarbonate (25 mL), saturated

copper sulfate (25 mL) and brine (25 mL), dried over $MgSO_4$ and evaporated to dryness (CARE: Product is volatile) to give the title compound as a colourless oil (2.6 g, 23 mmol, 45%); R_f (20% EtOAc/ light petroleum) 0.14; ν_{max} (film)/cm^{-1} 2975.8, 2929.7, 1649.5, 1618.8, 1424.2, 1398.6, 1373.0, 1183.5, 1101.6, 988.9, 922.3, 784.1; δ_H (300 MHz; $CDCl_3$) 3.26 (3H, s, NCH_3), 3.71 (3H, s, OCH_3), 5.75 (1H, dd, *J* 10.4, 2.1, H_2), 6.42 (1H, dd, *J* 17.1, 2.1, H_1), 6.74 (1H, dd, *J* 17.1, 10.4, H_3); δ_C (75.5 MHz; $CDCl_3$) 32.6 (NCH_3), 62.1 (OCH_3), 126.3 (=CH), 129.3 ($=CH_2$), 171.4 (C=O).

Identical to literature data.[150]

Synthesis of *N*-methoxy-*N*-methyl-3-phenylacrylamide 139



138

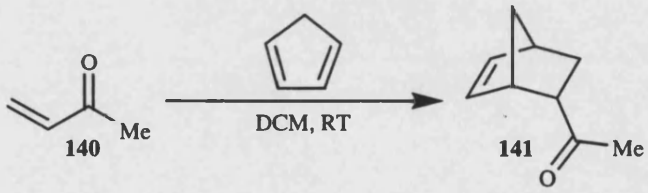
$C_{11}H_{13}NO_2$
Mol. Wt.: 191.23

Anhydrous pyridine (8.9 mL, 110 mmol, 2.2 Eq.) was added slowly to a stirred slurry of N,O-methyl methoxylamine hydrochloride (5.1 g, 52 mmol, 1.04 Eq.) and cinnamoyl chloride (8.3 g, 50 mmol, 1 Eq.) in anhydrous DCM (70 mL) at 0 °C under nitrogen. The reaction was stirred at this temperature for 15 minutes then allowed to warm to room temperature for 2 hours. The reaction was quenched by adding 5% aqueous HCl (20 mL) and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with sodium bicarbonate (25 mL), and brine (25 mL), dried over $MgSO_4$ and evaporated to dryness to give the title compound as an oil which crystallises on standing to give a white solid (9.6 g, 49

mmol, 97%); R_f (20% EtOAc/ light petroleum) 0.14; ν_{max} (nujol)/cm^{-1} 3057.8, 2986.1, 2929.7, 1649.5, 1618.8, 1577.8, 1485.6, 1460.0, 1413.9, 1383.2, 1209.1, 1178.4, 1142.5, 1096.4, 994.0, 958.2, 855.8, 789.2, 768.7, 697.0, 676.5; δ_H (300 MHz; $CDCl_3$) 3.31 (3H, s, NCH_3), 3.77 (3H, s, OCH_3), 7.07 (1H, d, *J* 15.8, =CHC=O), 7.35-7.42 (3H, m, Ar-H), 7.55-7.59 (2H, m, Ar-H), 7.74 (1H, d, =CHAr); δ_C (75.5 MHz; $CDCl_3$) 32.9 (NCH_3), 62.3 (OCH_3), 115.8 (CH), 128.0 (CH), 128.8 (CH), 129.6 (CH), 135.1 (Ar-C), 143.4 (CH), 167.3 (C=O).

Identical to literature data.[146]

Synthesis of 1-bicyclo[2.2.1]hept-5-ene-2-yl-ethanone 141



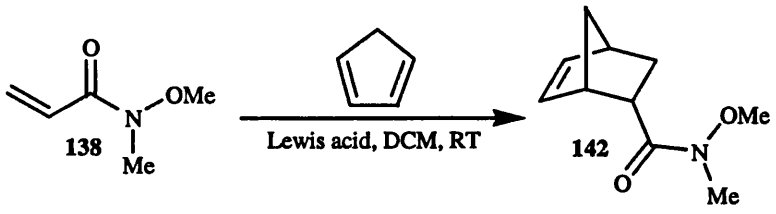
$C_9H_{12}O$
Mol. Wt.: 136.19

Freshly distilled cyclopentadiene monomer (0.8 mL, 10 mmol, 5 Eq.) was added to a stirred solution of methyl vinyl ketone (0.2 mL (90% technical grade), 2 mmol, 1 Eq.) in DCM (5 mL) under nitrogen. The reaction was stirred at room temperature over night. The solvent was removed *in vacuo* and the title compound isolated by column chromatography (10% EtOAc/ light petroleum) as a colourless oil (0.27 g, 2 mmol, 99%); R_f (20% EtOAc/ light petroleum) 0.50; υ_{max} (film)/cm^{-1} 2969.6, 2940.0, 2858.0, 1705.8, 1449.8, 1424.2, 1362.7, 1342.3, 1265.4, 1193.7, 1173.3, 1065.7, 1040.1, 1009.4, 942.8, 840.4, 814.8, 722.6; *endo* isomer: δ_H (300 MHz; $CDCl_3$) 0.82-0.93

(2H, m, CH), 1.42-1.54 (2H, m, CH_2), 1.71-1.79 (1H, m, CH), 2.14 (3H, s, CH_3), 2.90 (1H, brd d, CH), 2.99-3.04 (1H, m, CH), 3.25 (1H, brd d, CH), 5.86 (1H, dd, J 5.7, 2.8, =CH), 6.17 (1H, dd, J 5.7, 3.1, =CH); *exo* isomer: δ_H (300 MHz; $CDCl_3$) 0.83-0.90 (2H, m, CH), 1.33 (1H, brd d, CH), 1.83-1.92 (1H, m, CH), 2.22 (3H, s, Me), 2.38 (1H, dd, *J* 8.9, 4.7, CH), 2.89 (1H, brd d, CH), 2.99 (1H, brd d, CH), 6.12-6.18 (2H, m, =CH).

Identical to literature data.[147]

Synthesis of *N*-Methoxy-*N*-methylbicylco[2.2.1]hept-5-ene-carboxamide 142



$C_{10}H_{15}NO_2$
Mol. Wt.: 181.23

Weinreb acrylamide **138** (230 mg, 2 mmol, 1 Eq.) was added to a stirred suspension of anhydrous $Cu(OTf)_2$ (72 mg, 0.2 mmol, 10 mol%) in anhydrous DCM at –5 °C under nitrogen. Freshly prepared cyclopentadiene monomer (0.8 mL, 10 mmol, 5 Eq.) was added to the resultant blue solution and the reaction stirred for 40 hours. The reaction was washed with water (5 mL) and the aqueous layer extracted with DCM (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc/ light petroleum to 33% EtOAc/ light petroleum). To give the title compound as a colourless oil (312 mg, 1.7 mmol, 86%); R_f (20% EtOAc/ light petroleum) 0.12, 0.16; ν_{max}

(film)/cm^{-1} 3057.8, 2975.8, 2940.0, 2868.3, 1777.5, 1664.9, 1454.9, 1424.2, 1373.0, 1332.0, 1301.3, 1178.4, 1091.3, 1004.3, 973.5, 901.9, 830.2, 773.8, 712.4; *endo* isomer: δ_H (300 MHz; $CDCl_3$) 1.30-1.33 (1H, m, C*H*H), 1.40-1.46 (2H, m, CH_2), 1.86-1.95 (1H, m, CH), 2.89 (1H, brd d, *J* 0.9, CH), 3.15 (3H, s, NCH_3), 3.18 (2H, brd s, CH), 3.72 (3H, s, OCH_3), 5.96 (1H, dd, *J* 5.6, 2.5, =CH), 6.18 (1H, dd, *J* 5.6, 3.1, =CH); δ_C (75.5 MHz; $CDCl_3$) 30.3 (CH_2), 32.8 (CH), 41.4 (NCH_3), 42.9 (CH), 46.0 (CH), 50.2 (CH2), 61.5 (OCH_3), 132.7 (=CH), 136.8 (=CH), 176.2 (C=O); *exo* isomer: δ_H (300 MHz; $CDCl_3$) 1.34-1.41 (2H, m, CH_2), 1.68 (1H, d, *J* 8.1, CH), 1.83-1.89 (1H, m, CH), 2.52 (1H, brd s, CH), 2.92 (2H, d *J* 8.5, CH), 3.20 (3H, s, NMe), 3.68 (3H, s, OMe), 6.12-6.18 (2H, m, =CH); δ_C (75.5 MHz; $CDCl_3$) 30.7 (CH_2), 32.5 (CH), 39.8 (NMe), 41.6 (CH), 46.1 (CH), 46.5 (CH_2), 61.2 (OMe), 136.2 (=CH), 138.2 (=CH), 177.0 (C=O).

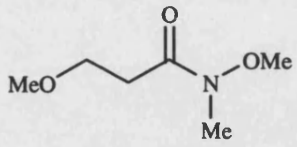
Identical to literature data.[150]

General procedure (17) for cycloadditions utilising BOX ligands

Anhydrous $Cu(OTf)_2$ (33 mg, 0.09 mmol, 9 mol%) was added to a stirred solution of BOX ligand (35 mg, 0.1 mmol, 10 mol%) in anhydrous DCM (2 mL) at room temperature under nitrogen. The resultant green solution was stirred well for 2 hours and then cooled to –5 °C. The requisite dienophile (1 Eq.) and freshly prepared cyclopentadiene monomer (0.4 mL, 5 mmol, 5 Eq.) were added and the reaction stirred at this temperature for 18 hours. The reaction was diluted with DCM (10 mL) and washed with water (5 mL). The aqueous layer was extracted with DCM (3 x 5 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*.

Analysis of the crude ^{1}H NMR spectra allowed determination of any increase in selectivity for the reaction.

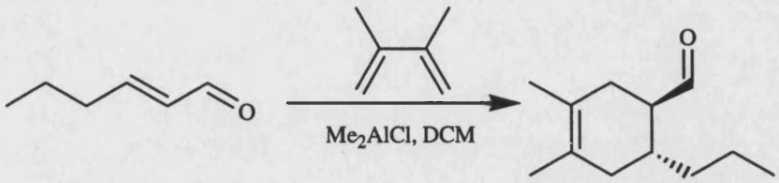
Attempted methanolysis of *N*-Methoxy-*N*-methylacrylamide 138



$C_6H_{13}NO_3$
Mol. Wt.: 147.17

Sodium hydride (48 mg, (60% w/w in mineral oil), 1.2 mmol, 1.2 Eq.) was added to a solution of anhydrous methanol (45 μL, 1.1 mmol, 1.1 Eq.) in anhydrous DCM (5 mL) at room temperature under nitrogen. After 30 minutes, Weinreb acrylamide **138** (0.12 g, 1 mmol, 1 Eq.) was added and the reaction was stirred overnight. The reaction was quenched by addition of 1M HCl (10 mL) and the aqueous layer extracted with DCM (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (90% EtOAc/ light petroleum) allowed isolation of the conjugate addition product **145** as a colourless oil (68 mg, 46%, 0.46 mmol); R_f (90% EtOAc/ light petroleum) 0.25; δ_H (300 MHz; $CDCl_3$) 2.72 (2H, t, *J* 6.2, CH_2), 3.20 (3H, s, CH_3), 3.36 (3H, s, OCH_3), 3.68-3.76 (5H, m, CH_2 & OCH_3).

Synthesis of 3,4-dimethyl-6-propyl-cyclohex-3-enecarbaldehyde 147 utilising Me_2AlCl as a catalyst

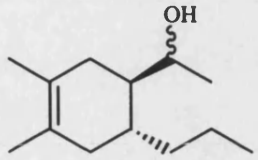


147
$C_{12}H_{20}O$
Mol. Wt.: 180.29

Me_2AlCl (0.5 mL, (1.0M solution in hexanes), 0.5 mmol, 10 mol%) was added slowly to a stirred solution of *trans*-2-hexenal (0.6 mL, 5 mmol, 1 Eq.) in anhydrous DCM (20 mL) under nitrogen at room temperature. 2,3-Dimethylbutadiene (1.1 mL, 10 mmol, 5 Eq.) was added to the resultant yellow solution and the reaction stirred for three hours. The reaction was washed with 1M HCl (2 x 10 mL) and the organic extracts dried over $MgSO_4$ and evaporated to dryness. The title compound was purified by column chromatography (2% Et_2O/ light petroleum) and isolated as a colourless oil (0.54 g, 3 mmol, 60%); R_f (10% Et_2O/ light petroleum) 0.41; υ_{max} (film)/cm^{-1} 2955.3, 2929.7, 2868.3, 1726.3, 1439.5, 1367.5, 1060.6, 1029.9, 1014.5; δ_H (300 MHz; $CDCl_3$) 0.90 (3H, t, *J* 6.6, alkyl CH_3), 1.19-1.46 (4H, m, alkyl CH_2), 1.60 (3H, s, $=CCH_3$), 1.64 (3H, s, $=CCH_3$), 1.70-1.72 (1H, m, CH), 1.96-2.31 (5H, m, CH & cyclic CH_2), 9.60 (1H, d, *J* 3.0 C=O); *m/z* (FAB$^-$) 181.0 (MH^+, 28%), 162.0 (M-H_2O, 23%), 139.0 (M-C_3H_5, 41%), 120.0 (C_9H_{12}, 26%), 97.0 (C_7H_{13}, 100%).

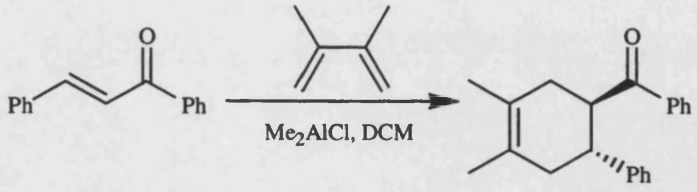
In addition, the secondary alcohol **148** could also be isolated (279 mg, 1.4 mmol, 28%); Rf (33% EtOAc/ light petroleum) 0.62; δ_H (300 MHz; $CDCl_3$) 0.90 (3H, m,

alkyl CH_3), 1.14-1.78 (15H, m, CH, CH_2 &CH_3), 1.91-2.15 (3H, m, CH & CH_2), 3.49-3.59 (1H, m, CH), 3.90-4.02 (2H, m, CH).



$C_{13}H_{24}O$
Mol. Wt.: 196.33

Synthesis of (3,4-dimethyl-6-phenyl-cyclohex-3-enyl)-phenyl-methanone 150

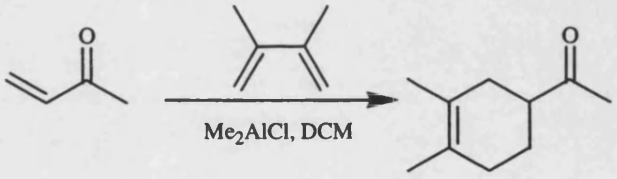


150
$C_{21}H_{22}O$
Mol. Wt.: 290.40

Me_2AlCl (2mL, (1.0M solution in hexanes), 0.002 mol, 10 mol%) was added slowly to a stirred solution of chalcone (4.2 g, 0.02 mol, 1 Eq.) in anhydrous DCM (30 mL) under nitrogen at room temperature. After stirring for 15 minutes at this temperature, 2,3-dimethylbutadiene (2.5 mL, 0.022 mol, 1.1 Eq.) was added to the resultant yellow solution and the reaction stirred for 18 hours. The reaction was washed with 1M HCl (2 x 10 mL) and the organic extracts dried over $MgSO_4$ and evaporated to dryness to give the title compound as a white solid (5.5 g, 0.019 mol, 95%); Mp 78-79 °C (lit.[148] 83-86 °C); R_f (20% EtOAc/ light petroleum) 0.67; υ_{max} (nujol)/cm^{-1} 3021.9, 2974.4, 2911.6, 2832.0, 1670.7, 1597.1, 1580.8, 1494.4, 1448.3, 1380.2, 1312.8, 1297.2, 1270.7, 1237.0, 1199.1, 1184.1, 1114.5. 1080.0, 1051.1, 1032.5, 1019.1, 913.7. 879.0, 844.1, 793.4, 761.3, 722.4, 704.3, 690.8, 680.7; δ_H (300 MHz; $CDCl_3$) 1.68 (6H, s,

CH_3), 2.29 (4H, brd dd, CH_2), 3.24- 3.33 (1H, m, CHAr), 3.95- 4.05 (1H, m, CHC=O), 7.13-7.21 (4H, m, Ar-H), 7.34- 7.40 (2H, m, Ar-H), 7.46-7.51 (1H, m, Ar-H), 7.81-7.83 (2H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 18.7, 18.8 (CH3), 36.9 (CH_2), 40.7 (CH_2), 43.0 (CH), 47.4 (CH), 124.1, 125.7 (=CCH_3), 126.1, 127.4, 128.0, 128.3, 128.4, 132.7 (Ar-CH), 137.3, 144.6 (Ar-C), 203.5 (C=O); *m/z* (FAB) 291.1 (MH^+, 52%), 209.1 (7%), 199.1 (17%), 185.1 (M-C_7H_5O, 14%), 152.0 (7%), 133.1 (11%), 115.0 (7%), 105.0 (100%), 79.0 (6%) (Found: M^+ 290.1660. $C_{21}H_{22}O$ requires 290.1671) (Found: C, 86.5, H, 7.61. $C_{21}H_{22}O$ requires C, 86.9, H, 7.64).

Synthesis of 1-(3,4-dimethyl-cyclohex-3-enyl)-ethanone 151

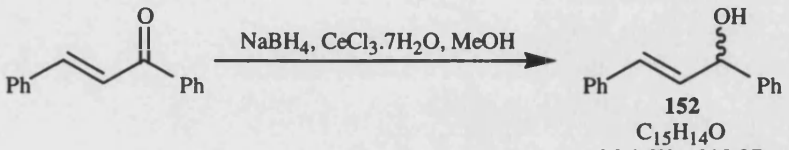


151
$C_{10}H_{16}O$
Mol. Wt.: 152.23

Methyl vinyl ketone (8.3 mL, 0.1 mol, 1 Eq.) was added slowly to a stirred solution of Me_2AlCl (10 mL (1.0M solution in hexanes), 0.01 mol, 10 mol%) (CARE: Gas evolution) in anhydrous DCM (50 mL) at 0 °C under nitrogen. The reaction was stirred at this temperature for 15 minutes and 2,3-dimethylbutadiene (13.6 mL, 0.12 mol, 1.2 Eq.) (CARE: Gas evolution) was added slowly. The reaction was allowed to warm to room temperature overnight when it was quenched by addition of 1M HCl (2 x 20 mL). The organic extracts were dried over $MgSO_4$ and evaporated to dryness. Purification of the crude material by vacuum distillation (89 °C/ 9 mmHg) gave the title compound as a colourless oil (10.2 g, 0.07 mol, 67%); R_f (20% EtOAc/ light

petroleum) 0.60; υ_{max} (film)/cm^{-1} 2994.4, 2927.7, 2832.4, 1712.6, 1450.5, 1374.2, 1355.2, 1293.2, 1231.3, 1164.6, 1116.9, 959.7; δ_H (300 MHz; $CDCl_3$) 1.55-1.59 (1H, m, CH), 1.61 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.92-2.14 (5H, m, CH and CH_2), 2.16 (3H, s, CH_3CO), 2.51-2.61 (1H, m, CH); δ_C (75.5 MHz; $CDCl_3$) 19.2, 19.4 (CH_3), 25.7 (CH_2), 28.3 (*H*CCO), 31.6, 33.5 (CH_2), 48.6 (OC*C*H$_3$), 124.3, 125.8 (=*C*CH$_3$), 212.2 (C=O); *m/z* (EI) 151.1 (M^+, 100%), 133.0 (17%), 123.0 (26%), 107.1 (60%), 95.0 (18%), 81.0 (7%), 71.0 (13%), 61.0 (20%).

Synthesis of 1,3-diphenyl prop-2-en-1-ol 152

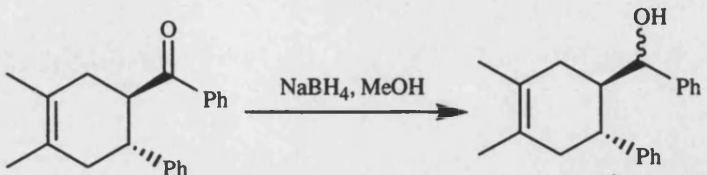


152
$C_{15}H_{14}O$
Mol. Wt.: 210.27

$NaBH_4$ (0.76 g, 0.02 mol, 1 Eq.) was added portionwise to a stirred solution of chalcone (4.2 g, 0.02 mol, 1 Eq.) and $CeCl_3.7H_2O$ (7.5 g, 0.02 mol, 1 Eq.) in MeOH (150 mL) at 0 °C. After 10 minutes the reaction was quenched by addition of water (50 mL) and extracted with diethyl ether (3 x 70 mL). The combined organic extracts were dried over MgSO4 and concentrated *in vacuo*. Recrystallisation from DCM/ light petroleum gave the title compound as a white solid (3.2 g, 0.015g, 75%); Mp 52-54 °C; R_f (20% EtOAc/ light petroleum) 0.34; υ_{max} (nujol)/cm^{-1} 3349.6, 3093.6, 3062.9, 3037.3, 1598.3, 1577.8, 1490.8, 1454.9, 1434.4, 1393.5, 1352.5, 1270.6, 1168.1, 1101.6, 1065.7, 1014.5, 963.3, 804.5, 748.2; δ_H (300 MHz; $CDCl_3$) 2.45 (1H, brd d, OH), 5.30 (1H, dd, *J* 6.3, 2.2, CH), 6.33 (1H, dd, *J* 15.8, 6.5, =C*H*CH), 6.63 (1H, d, *J* 15.8, =C*H*Ar), 7.17-7.40 (10H, m, Ar-H).

Identical to literature data.[149]

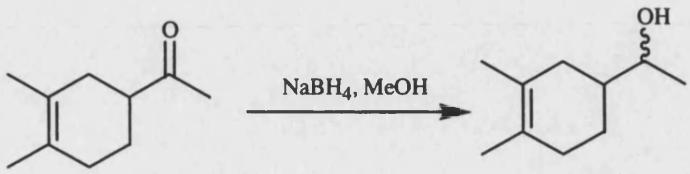
Synthesis of (3,4-dimethyl-6-phenyl-cyclohex-3-enyl)-phenyl-methanol 153



153
$C_{21}H_{24}O$
Mol. Wt.: 292.41

$NaBH_4$ (0.19 g, 5 mmol, 1 Eq.) was added portionwise to a stirred solution of ketone **150** in DCM (5 mL) and MeOH (50 mL) at 0 °C. After 30 minutes the reaction was quenched with water (20 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was purified by column chromatography (10% EtOAc/ light petroleum) and isolated as a viscous oil (1.3 g, 4.3 mmol, 86%); R_f (20% EtOAc/ light petroleum) 0.47; ν_{max} (film)/cm^{-1} 3390.6, 3062.9, 3027.0, 2975.8, 2904.1, 2847.8, 1493.2, 1495.9, 1449.8, 1029.9, 1004.3, 763.6, 707.3; δ_H (300 MHz; $CDCl_3$) 1.56-1.63 (7H, m, CH & CH_3), 1.72 (1H, d, *J* 2.7, OH), 1.84-1.89 (1H, m, CH), 2.16-2.39 (3H, m, CH & CH_2), 2.88 (1H, q, *J* 7.9, CH), 4.68 (1H, dd, *J* 6.5, 2.4, CH), 7.06-7.36 (10H, m, Ar-H); δ_C (75.5 MHz; $CDCl_3$) 18.5, 18.9 (=C*C*H_3), 31.6, 39.3 (CH_2), 45.7 (CH), 75.9 (CHOH), 124.5, 124.7 (=C), 126.3, 127.0, 127.4, 127.8, 128.0, 128.6 (Ar-CH), 142.6, 145.9 (Ar-C); *m/z* (EI) 292.2 (M^+, 41%), 274.2 (M-H_2O, 14%), 180.1 (70%), 170.1 (9%), 105.0 (32%), 91.1 (73%), 61.0 (47%), 43.0 (C_3H_7, 100%), 28.8 (15%) (Found: M^+ 292.1824. $C_{21}H_{24}O$ requires 292.1827).

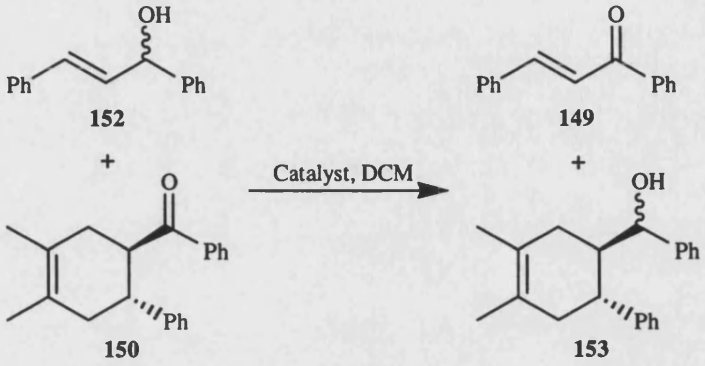
Synthesis of 1-(3,4-dimethyl-cyclohex-3-enyl)-ethanol 154



154
$C_{10}H_{18}O$
Mol. Wt.: 154.25

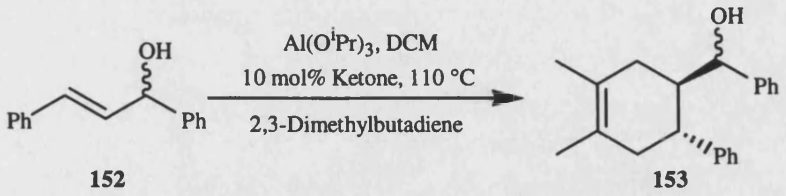
The title compound was synthesis in a similar manner to reduced (3,4-dimethyl-6-phenyl-cyclohex-3-enyl)-phenyl-methanol **153** and isolated as a colourless oil (1.5 g, 7.7 mmol, 86%); R_f (20% EtOAc/ light petroleum) 0.33; υ_{max} (film)/cm^{-1} 3359.9, 2960.5, 2919.5, 2827.3, 1746.8, 1726.3, 1434.4, 1373.0, 1101.6, 1239.8, 1157.9, 1101.6, 1065.7, 947.9, 891.6, 855.8, 779.0, 686.8; δ_H (300 MHz; $CDCl_3$) 1.19 (3H, dd, *J* 6.3, 1.7, CH_3), 1.12-1.17 (1H, m, CH or OH), 1.49-1.51 (1H, m, CH or OH), 1.61 (6H, s, $=CCH_3$), 1.67-2.03 (6H, m, 3 x CH_2), 3.60 (1H, ddq, *J* 25.1, 6.3, 6.3, *H*COH); δ_H (75.5 MHz; $CDCl_3$) 18.7, 19.2 (CH_3), 26.6, 20.8 (CH), 25.3, 25.7, 31.8, 33.6, 34.3 (CH_2), 42.0, 42.1 (CH_3), 124.6, 124.7, 125.5, 125.8 (=C); *m/z* (FAB) 154.2 (M^+, 17%), 136.1 (16%), 121.1 (50%), 107.1 (100%), 93.1 (55%), 79.1 (36%), 67.1 (51%), 53.0 (26%), 41.0 (76%), 26.7 (55%) (Found M^+ 154.1362. $C_{10}H_{18}O$ requires 154.1358).

General procedure (18) for the $Al(O^iPr)_3$ catalysed transfer hydrogenation between 1,3-diphenyl prop-2-en-ol 152 and (3,4-dimethyl-6-phenyl-cyclohex-3-enyl)-phenyl-methanone 150



$Al(O^iPr)_3$ (245 mg, 1.2 mmol, 1.2 Eq.) in anhydrous DCM (2 mL) was added dropwise to a stirred solution of 1,3-diphenyl prop-2-en-ol **152** (210 mg, 1 mmol, 1 Eq.) in anhydrous DCM (5mL) at reflux under nitrogen. After stirring for 20 minutes, (3,4-dimethyl-6-phenyl-cyclohex-3-enyl)-phenyl-methanone **150** (290 mg, 1 mmol, 1 Eq.) in anhydrous DCM (4 mL) was added. After 18 hours the reaction was quenched by slow addition of saturated ammonium chloride (1.2 mL). Diethyl ether (30 mL) was added and the precipitated aluminium salts were dissolved by careful addition of 10% HCl. The aqueous layer was washed with diethyl ether (3 x 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Analysis of the ^1H NMR of the crude reaction mixture allowed determination of any transfer hydrogenation.

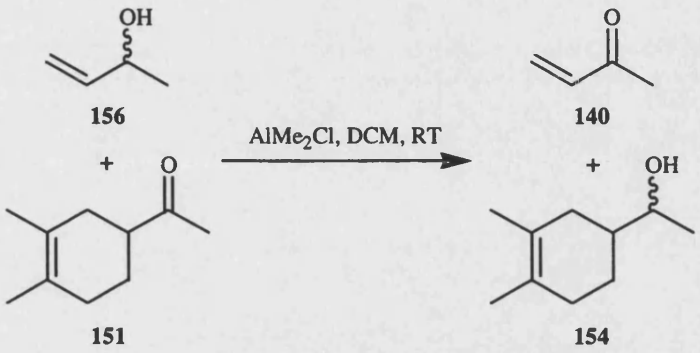
General procedure (19) for the Al(O^{i}Pr)$_3$ catalysed tandem Diels-Alder MVPO reaction of 1,3-diphenyl prop-2-en-ol 152



152 **153**

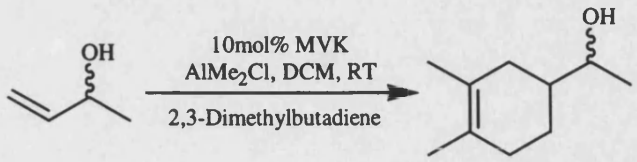
Al(O^{i}Pr)$_3$ (245 mg, 1.2 mmol, 1.2 Eq.) in anhydrous DCM (2 mL) was added dropwise to a stirred solution of 1,3-diphenyl prop-2-en-ol **152** (210 mg, 1 mmol, 1 Eq.) in anhydrous DCM (5mL) at room temperature under nitrogen in a oven dried pressure tube. After stirring for 20 minutes, the requisite ketone (10 mol%) in anhydrous DCM (4 mL) was added and the reaction was heated to reflux (oil bath 110 °C). After 18 hours the reaction was quenched by slow addition of saturated ammonium chloride (1.2 mL). Diethyl ether (30 mL) was added and the precipitated aluminium salts were dissolved by careful addition of 10% HCl. The aqueous layer was washed with diethyl ether (3 x 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Analysis of the ^{1}H NMR of the crude reaction mixture allowed determination of any reaction.

General procedure (20) for the $AlMe_2Cl$ catalysed transfer hydrogenation between reduced prop-2-en-1-ol 156 and 1-(3,4-dimethyl-cyclohex-3-enyl)-ethanone 151



$AlMe_2Cl$ (0.1 mL (1.0M solution in hexanes), 0.1 mmol, 10 mol%) was added dropwise to a stirred solution of prop-2-en-1-ol **156** (86 μL, 1 mmol, 1 Eq.) in anhydrous DCM (5mL) at room temperature under nitrogen. After stirring for 20 minutes, 1-(3,4-dimethyl-cyclohex-3-enyl)-ethanone **151** (152 mg, 1 mmol, 1 Eq.) in anhydrous DCM (3 mL) was added. After 18 hours the reaction was quenched by slow addition of saturated ammonium chloride (0.1 mL). Diethyl ether (30 mL) was added and the precipitated aluminium salts were dissolved by careful addition of 10% HCl. The aqueous layer was washed with diethyl ether (3 x 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Analysis of the ^1H NMR of the crude reaction mixture allowed determination of any transfer hydrogenation.

General procedure (21) for the $AlMe_2Cl$ catalysed tandem Diels-Alder MVPO reaction of prop-2-en-1-ol 156



156 **154**

$AlMe_2Cl$ (0.5 mL (1.0M solution in hexanes), 0.5 mmol, 10 mol%) was added dropwise to a stirred solution of prop-2-en-1-ol **156** (0.43 mL, 5 mmol, 1 Eq.) in anhydrous DCM (5mL) at room temperature under. After stirring for 20 minutes, methyl vinyl ketone (40 μL, 0.5 mmol, 10 mol) was added and the reaction. After 18 hours the reaction was quenched by slow addition of saturated ammonium chloride (0.5 mL). Diethyl ether (30 mL) was added and the precipitated aluminium salts were dissolved by careful addition of 10% HCl. The aqueous layer was washed with diethyl ether (3 x 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Analysis of the ^1H NMR of the crude reaction mixture allowed determination of any reaction.

Chapter 6

References

6) References

[1] Diels, O., Alder, K.; *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

[2] a) Oppolzer, W.; In *Comprehensive Organic Synthesis*, Eds. Trost, B. M., Flemming, I.; Pergamon Press: Oxford, **1991**, *5*, 315; b) Carruthers, W.; "Cycloaddition reactions in Organic Synthesis"; Pergamon Press: Oxford, **1990**.

[3] a) Waldman, H., *Synthesis* **1994**, 536; b) Buonora, P., Olsen, J-C., Oh, T.; *Tetrahedron* **2001**, *57*, 6099.

[4] Fallis, A. G.; *Acc. Chem. Res.* **1999**, *32*, 464.

[5] Joshel, L. M., Butz, L. W.; *J. Am. Chem. Soc.* **1941**, *63*, 3350.

[6] Squillacote, M. E., Sheridan, R. S., Chapman, O. L., Anet, F. A. L.; *J. Am. Chem. Soc.* **1979**, *101*, 3657.

[7] Flemming, I.; "Frontier Orbitals and Organic Chemical Reactions"; Wiley: London, **1976**, Chapter 4.

[8] Alder, K., Stein, G.; *Justus Liebigs Ann. Chem.* **1933**, *504*, 216.

[9] Pindur, U., Lutz, G., Otto, C.; *Chem. Rev.* **1993**, *93*, 741.

[10] a) Dias, L. C.; *J. Braz. Chem. Soc.* **1997**, *8*, 289; b) Regan, A. C.; *Contemporary Organic Synthesis*, **1997**, *4*, 1; c) Regan, A. C.; *J. Chem. Soc., Perkin Trans. 1* **1998**, 1151; d) Regan, A. C.; *J. Chem. Soc., Perkin Trans. 1* **1999**, 357; e) Kagan, H. B., Raint, O.; *Chem. Rev.* **1992**, *92*, 1007.

[11] a) Oppolzer, W.; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876; b) Helmchen, G., Karge, R., Weetman, J.; In *Modern Synthetic Methods*, Ed. Sheffold, R.; Springer-Verlag: New York, **1986**, *4*, 262.

[12] Prelog, V.; *Helv. Chim. Acta.* **1953**, *36*, 308.

[13] Walborsky, H. M., Barash, L., Davis, T. C.; *Tetrahedron* **1963**, *19*, 2333.

[14] Oppolzer, W., Kurth, M., Reichlin, Moffatt, F.; *Tetrahedron Lett.* **1981**, *22*, 2545.

[15] a) Corey, E. J., Ensley, H. E.; *J. Am. Chem. Soc.* **1975**, *97*, 6908; b) For the formation of **15** using a chiral Lewis acid see Corey, E. J., Imai, N., Pikul, S.; *Tetrahedron Lett.* **1991**, *32*, 7517.

[16] Whitesell, J. K.; *Chem. Rev.* **1992**, *92*, 953.

[17] Oppolzer, W.; *Tetrahedron* **1987**, *43*, 1969.

[18] Oppolzer, W., Chapuis, C., Dupuis, D., Guo, M.; *Helv. Chim. Acta* **1985**, *68*, 2100.

[19] a) Choy, W., Reed III, L. A., Masamune, S. J.; *J. Org. Chem.* **1983**, *48*, 1137; b) Masamune, S. J., Reed III, L. A., Davis, J. T., Choy, W.; *J. Org. Chem.* **1983**, *48*, 4441.

[20] Poll, T., Helmchen, G., Bauer, B.; *Tetrahedron Lett.* **1984**, *25*, 2191.

[21] Poll, T., Metter, J. O., Helmchen, G.; *Angew. Chem. Intl. Ed. Engl.* **1985**, *97*, 112.

[22] Poll, T., Sobczak, A., Hartmann, H., Helmchen, G.; *Tetrahedron Lett.* **1985**, *26*, 3095.

[23] Poll, T., Abdel Hady, A. F., Karge, R., Linz, J., Weetman, J., Helmchen, G.; *Tetrahedron Lett.* **1989**, *30*, 5595.

[24] a) Miyaji, K., Ohara, Y., Takahashi, Y., Tsuruda, T., Arai, K.; *Tetrahedron Lett.* **1991**, *32*, 4557; b) Helmchen, G., Ihrig, K., Schindler, H.; *Tetrahedron Lett.* **1987**, *28*, 183; c) Hansen, M. M. *et al*; *J. Org. Chem.* **1998**, *63*, 775.

[25] Loupy, A., Monteux, D.; *Tetrahedron Lett.* **1996**, *37*, 7023.

[26] Akiyama, T., Horiguchi, N., Ida, T., Ozaki, S.; *Chem. Lett.* **1995**, 975; b) Ferreira, M. L. G., Pinheiro, S., Perrone, C. C., Costa, P. R. R., Ferreira, V. F.; *Tetrahedron: Asymmetry* **1998**, *9*, 2671.

[27] Nieman, J. A., Keay, B. A.; *Tetrahedron: Asymmetry* **1996**, *7*, 3521.

[28] Burke, M. J., Allan, M. M., Parvez, M., Keay, B. A.; *Tetrahedron: Asymmetry* **2000**, *11*, 2733.

[29] Oppolzer, W., Lienard, P.; *Helv. Chim. Acta.* **1992**, *72*, 2572.

[30] Oppolzer, W., Seletsky, B. M., Bernardinelli, G.; *Tetrahedron Lett.* **1994**, *35*, 3509.

[31] a) Boeckman, Jr., R. K., Nelson, S. G., Gaul, M. D.; *J. Am. Chem. Soc.* **1992**, *114*, 2258; b) Boeckman, Jr., R. K., Liu, Y.; *J. Org. Chem.* **1996**, *61*, 7984;c) Boeckman, Jr., R. K., Laci, M. A., Johnson, A. T.; *Tetrahedron: Asymmetry* **2001**, *12*, 205.

[32] Studer, A.; *Synthesis* **1996**, 793.

[33] Enders, D., Klatt, M.; *Synthesis* **1996**, 1403.

[34] Lamy-Schelkens, H., Ghosez, L.; *Tetrahedron Lett.* **1989**, *30*, 5891.

[35] Waldmann, H.; *J. Org. Chem.* **1988**, *53*, 6133.

[36] Tomioka, K., Suenaga, T., Koga, K.; *Tetrahedron Lett.* **1986**, *27*, 369.

[37] Tomioka, K., Hamada, N., Suenaga, T., Koga, K.; *J. Chem. Soc., Perkin Trans. 1* **1990**, 426.

[38] Ikota, N.; *Chem. Pharm. Bull.* **1989**, *37*, 2219.

[39] Camps, P., Font-Bardia, M., Giménez, Pérez, F., Solans, X., Soldevilla, N.; *Tetrahedron: Asymmetry* **1999**, *10*, 3123.

[40] Bueno, M. P., Cativela, C. A., Mayoral, J. A.; *J. Org. Chem.* **1991**, *56*, 6551.

[41] Ager, D. J., Prakash, I., Schaad, D. R.; *Chem. Rev.* **1996**, *96*, 835.

[42] a) Pouihes, A., Uriarte, E., Kouklovsky, C., Langlois, N., Langlois, Y., Chiaroni, A., Riche, C.; *Tetrahedron Lett.* **1989**, *30*, 1395; b) Kouklovsky, C., Pouihes, A., Langlois, Y.; *J. Am. Chem. Soc.* **1990**, *112*, 6672; c) Langlois, Y., Pouihes, A.; *Tetrahedron: Asymmetry* **1991**, *2*, 1223.

[43] Dyen, M. E., Swern, D.; *Chem. Rev.* **1967**, *67*, 197.

[44] Ager, D. J., Prakash, I., Schaad, D. A.; *Aldrichimica Acta* **1997**, *30*, 3.

[45] Evans, D. A., Takacs, J. M., McGee, L. R., Ennis, M. D., Mathre, D. J., Bartroli, J.; *Pure & Appl. Chem.* **1981**, *53*, 1109.

[46] a) Evans, D. A., Chapman, K. T., Bisaha, J.; *J. Am. Chem. Soc.* **1984**, *106*, 4261; b) Evans, D. A., Chapman, K. T., Bisaha, J.; *Tetrahedron Lett.* **1984**, *25*, 4071; c) Evans, D. A., Chapman, K. T., Hung, D. T., Kawaguchi, A. T.; *Angew. Chem. Intl. Ed. Engl.* **1987**, *26*, 1184; d) Evans, D. A., Chapman, K. T., Bisaha, J.; *J. Am. Chem. Soc.* **1988**, *110*, 1238.

[47] a) Sibi, M. P.; *Aldrichimica Acta* **1999**, *32*, 93; b) Sibi, M. P., Prasad, K. D., Jianguo, J.; *Tetrahedron Lett.* **1995**, *36*, 8965.

[48] Evans, D. A., Ennis, M. D., Mathre, D. J.; *J. Am. Chem. Soc.* **1982**, *104*, 1737.

[49] Evans, D. A., Ellman, J. A., Dorow, R. L.; *Tetrahedron Lett.* **1987**, *28*, 1123.

[50] Evans, D. A., Sjogren, E. B., Bartroli, J., Dow, R. L.; *Tetrahedron Lett.* **1986**, *27*, 4957.

[51] Evans, D. A., Britton, T. C., Ellman J. A.; *Tetrahedron Lett.* **1987**, *28*, 6141.

[52] a) Delair, P., Einhorn, C., Einhorn, J., Luche, J. L.; *J. Org. Chem.* **1994**, *59*, 4680; b) Bull, S. D., Davies, S. G., Jones, S., Polywka, M. E. C., Prasad, R. S., Sanganee, H. J.; *Synlett* **1998**, 519.

[53] Davies, S. G., Sanganee, H. J.; *Tetrahedron: Asymmetry* **1995**, *6*, 671.

[54] Davies, I. W., Senanayake, C. H., Castonguay, L., Larsen, R. D., Verhoeven, T. R., Reider, P. J.; *Tetrahedron Lett.* **1995**, *36*, 7619.

[55] Sudo, A., Saigo, K.; *Tetrahedron: Asymmetry* **1996**, *7*, 2939.

[56] Sudo, A., Saigo, K.; *Chem. Lett.* **1997**, 97.

[57] Banks, M. R., Blake, A. L., Cadogan, J. I. G., Doyle, A. A., Gosney, I., Hodgson, P. K. G., Thorburn, P.; *Tetrahedron* **1996**, *52*, 4079.

[58] a) Matsunaga, H., Kirura, K., Ishizuka, T., Haratake, M., Kunieda, T.; *Tetrahedron Lett.* **1991**, *32*, 7715; b) Kimura, K., Murata, K., Otsuka, K., Ishizuka, T., Haratake, M., Kunieda, Y.; *Tetrahedron Lett.* **1992**, *33*, 4461; c) Hashimoto, N., Ishizuka, T., Kunieda, T.; *Tetrahedron Lett.* **1994**, *35*, 721; d) Nakamura, T., Hashimoto, N., Ishizuka, T., Kunieda, T.; *Tetrahedron Lett.* **1997**, *38*, 559.

[59] Carreno, C. M.; *Chem. Rev.* **1995**, *95*, 1717.

[60] a) Arai, Y., Masuda, T., Masaki, Y.; *Chem. Lett.* **1997**, 145; b) Arai, Y., Masuda, T., Masaki, Y.; *J. Chem. Soc., Perkin Trans. 1* **1999**, 2165.

[61] Jones, S., Atherton, J. C. C.; *Tetrahedron: Asymmetry* **2001**, *12*, 1117.

[62] Frühauf, H-W.; *Chem. Rev.* **1997**, *97*, 523.

[63] Wulff, W. D., Bauta, W. E., Kaesler, R. W., Lankford, P. J., Miller, R. A., Murray, C. A., Yang, D. C.; *J. Am. Chem. Soc.* **1990**, *112*, 3642.

[64] Barluenga, J., Tomás, M., López-Pelegrín, J. A., Rubio, E.; *Tetrahedron Lett.* **1997**, *38*, 3981.

[65] Rahm, A., Rheingold, A. L., Wulff, W. D.; *Tetrahedron* **2000**, *56*, 4951.

[66] Davies, S. G.; *Chemistry In Britain* **1989**, *25*, 268.

[67] Davies, S. G., Dordor-Hedgecock, I. M., Sutton, K. H., Walker, J. C., Bourne, C., Jones, R. H., Prout, K.; *J. Chem. Soc., Chem. Commun.* **1986**, 607.

[68] Davies, S. G., Walker, J. C.; *J. Chem. Soc., Chem. Commun.* **1986**, 609.

[69] a) Westwell, A. D., Williams, J. M. J.; *J. Chem. Soc., Chem. Comm.* **1994**, 2501; b) Westwell, A. D., Williams, J. M. J.; *J. Chem. Soc., Perkin Trans. 1* **1996**, 1; c) Westwell, A. D., Williams, J. M. J.; *Tetrahedron* **1997**, *53*, 13063.

[70] a) Clapham, G., Shipman, M.; *Tetrahedron Lett.* **1999**, *40*, 5639; b) Clapham, G., Shipman, M.; *Tetrahedron* **2000**, *56*, 1127.

[71] Eiber, E., Höcht, P., Prantl, B., Roßmaier, H., Schuhbauer, H., Wiest, H., Sauer, J.; *Liebigs Ann. Chem.* **1997**, 2471.

[72] Alfonso, C.; *Unpublished Results* **1998**.

[73] Sauer, J., Sustmann, R.; *Angew. Chem. Intl. Ed. Engl.* **1980**, *19*, 779.

[74] March, J.; "Advanced Organic Synthesis"; Wiley: London, 4th Edition, **1992**, Chapter 10, Page 339.

[75] a) Holmberg, K., Hansen, B.; *Tetrahedron Lett.* **1975**, *27*, 2303; b) Sydnes, L. K., Sandberg, M.; *Tetrahedron* **1997**, *53*, 12679.

[76] a) Frost, C. G., Howarth, J., Williams, J. M. J.; *Tetrahedron: Asymmetry* **1992**, *3*, 1089; b) Consiglio, G., Waymouth, R. M.; *Chem. Rev.* **1989**, *89*, 257; Trost, B. M., Van Vranken, D. L.; *Chem. Rev.* **1996**, *96*, 395.

[77] a) Sprinz, J., Helmchen, G.; *Tetrahedron Lett.* **1993**, *34*, 1769; b) von Matt, P., Pfaltz, A.; *Angew. Chem. Int Ed. Engl.* **1993**, *32*, 566, c) Allen, J. V.,

Dawson, G. J., Frost, C. G., Williams, J. M. J.; *Tetrahedron*, **1994**, *50*, 799; d) Allen, J. V., Coote, S. J., Dawson, G. J., Frost, C. G., Martin, C. J., Williams, J. M. J.; *J. Chem. Soc., Perkin Trans. 1* **1994**, 1; e) Dawson, G. J., Frost, C. G., Williams, J. M. J.; *Tetrahedron Lett.* **1993**, *34*, 3149.

[78] Larock, R. C., Harrison, L. W., Hsu, M. H.; *J. Org. Chem.* **1984**, *49*, 3664.

[79] Tsuji, J., Saki, K., Nagashima, H., Shimizu, I.; *Tetrahedron Lett.* **1981**, *22*, 131.

[80] a) Bäckvall, J. E., Nordberg, R. E.; *J. Am. Chem. Soc.* **1981**, *103*, 4959; Trost, B. M., Verhoeven, T. R., Fortunak, J. M.; *Tetrahedron Lett.* **1979**, *25*, 2301.

[81] a) Janssen, J. P., Helmchen, G.; *Tetrahedron Lett.* **1997**, *38*, 8025; b) Takeuchi, R., Kashio M.; *J. Am. Chem. Soc.* **1998**, *120*, 8647; c) Fuji, K., Kinoshita, N., Tanaka, K., Kawabata, T.; *Chem. Comm.* **1999**, 2289.

[82] a) Takeuchi, R., Shiga, N.; *Org. Lett.* **1999**, *1*, 265; b) Takeuchi, R., Ue, N., Tanabe, K., Yamashita, K., Shiga, N.; *J. Am. Chem. Soc.* **2001**, *123*, 9525.

[83] Lombardo, L.; *Tetrahedron Lett.* **1985**, *26*, 381.

[84] Chung, Y., Duerr, B. F., McKelvey, T. A., Nanjappan, P., Czarnik, A. W.; *J. Org. Chem.* **1989**, *54*, 1018.

[84a] i) Amatore, C., Jutand, A., Khalil, F., M'Barki, M. A., Mottier, L.; *Organometallics* **1993**, *12*, 3168; ii) Herrmann, W. A., Thiel, W. R., Broßmer, C., Öfele, K., Priermeier, T., Scherer, W.; *J. Organomet. Chem.* **1993**, *461*, 51.

[85] a) Kobayashi, S., Hachiya, I., Takahori, T., Araki, M., Ishitani, H.; *Tetrahedron Lett.* **1992**, *33*, 6815; b) Kobayashi, S., Ishitani, H.; *J. Am.*

Chem. Soc. **1994**, *116*, 4083; c) Kobayashi, S., Ishitani, H., Hachiya, I., Araki, M.; *Tetrahedron* **1994**, *50*, 11623; d) Marshman, R. W.; *Aldrichimica Acta* **1995**, *28*, 77.

[86] Otera, J.; *Chem. Rev.* **1993**, *93*, 1449.

[87] Evans, D. A., Coleman, P. J., Dias, L. C.; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2738.

[88] Fukuzawa, S., Hongo, Y.; *Tetrahedron Lett.* **1998**, *39*, 3521.

[89] Orita, A., Nagano, Y., Hirano, J., Oreta, J.; *Synlett* **2001**, 637.

[90] Su, D. W., Wang, Y. C., Yan, T. H.; *Chem. Commun.* **1999**, 545.

[91] Hanamoto, T., Sugimoto, Y., Yokoyama, Y., Inanaga, J.; *J. Org. Chem.* **1996**, *61*, 4491.

[92] Sharma, G. V. M., Ilangovan, A.; *Synlett* **1999**, 1963.

[93] Sharma, G. V. M., Ilangovan, A., Mahalingam, A. K.; *J. Org. Chem.* **1998**, *63*, 9103.

[94] Barrett, A. G. M., Braddock, D. C.; *Chem. Commun.* **1997**, 351.

[95] a) Waller, F. J., Barrett, A. G. M., Braddock, D. C., McKinnell, R. M., Ramprasad, D.; J. Chem. *Soc., Perkin Trans. 1* **1999**, 867; b) Barrett, A. G. M., Braddock, D. C., Ducray, R., McKinnell, R. M., Waller, F. J.; *Synlett* **2000**, 57.

[96] Barrett, A. G. M., Braddock, D. C., Henschke, J. P., Walker, E. R.; *J. Chem. Soc., Perkin Trans. 1* **1999**, 873.

[97] Aspinall, H. C., Greeves, N., McIver, E. G.; *Tetrahedron Lett.* **1998**, *39*, 9283.

[98] a) Kobayashi, S., Ishitani, H., Nagayama, S.; *Chem. Lett.* **1995**, 423; b) Ma, Y., Qian, C., Wang, L., Yang, M.; *J. Org. Chem.* **2000**, *65*, 3864.

[99] Narasaka, K., Kusama, H., Hayashi, Y.; *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1471.

[100] Knol, J., Feringa, B. L.; *Syn. Commun.* **1996**, *26*, 261.

[101] Corey, E. J., Pikul, S.; *Org. Syn.* **1993**, *71*, 30.

[102] Thom, C., Kocieński, P.; *Synthesis* **1992**, 582.

[103] Ho, G. J., Mathre, D. J.; *J. Org. Chem.* **1995**, *60*, 2271.

[104] Ager, D. J., Allen, D. R., Schaad, D. R.; *Synthesis* **1996**, 1283.

[105] Aspinall, H. C., Dwyer, J. L. M., Greeves, N., McIver, E. G., Woolley, J. C.; *Organometallics* **1998**, *17*, 1884.

[106] Braddock, D. C., Wildsmith, A. J.; *Tetrahedron Lett.* **2001**, *42*, 3239.

[107] a) Blacker, A. J., Clarke, M. L., Loft, M. S., Williams, J. M. J.; *Org. Lett.* **1999**, *1*, 1969; b) Acemoglu, L., Williams, J. M. J.; *Adv. Synth. Catal.* **2001**, *1*, 343.

[108] Denmark, S. E., Wynn, T.; *J. Am. Chem. Soc.* **2001**, *123*, 6199.

[109] Furuta, K., Miwa, Y., Iwanaga, K., Yamamoto, H.; *J. Am. Chem. Soc.* **1988**, *110*, 6254.

[110] a) Ahrendt, K. A., Borths, C. J., MacMillan, D. W. C.; *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) Jen, W. S., Wiener, J. J. M., MacMillan, D. W. C.; *J. Am. Chem. Soc.* **2000**, *122*, 9874; c) Paras, N. A., MacMillan, D. W. C.; *J. Am. Chem. Soc.* **2001**, *123*, 4370.

[111] Nahm, S., Weinreb, S. M.; *Tetrahedron Lett.* **1981**, *22*, 3815.

[112] a) Mentzel, M., Hoffmann, H. M. R.; *J. Prakt. Chem.* **1997**, *339*, 517; b) Singh, J., Satyamurthi, N., Aidhen, I. S.; *J. Prakt. Chem.* **2000**, *342*, 340.

[113] a) Nuzillard, J. M., Boumendjel, A., Massiot, G.; *Tetrahedron Lett.* **1989**, *30*, 3779; b) Netz, D. F., Seidel, J. L.; *Tetrahedron Lett.* **1992**, *33*, 1957.

[114] a) Bennani, Y. L., Sharpless, K. B.; *Tetrahedron Lett.* **1993**, *34*, 2079; b) Hale, M. R., Hoveyda, A. H.; *J. Org. Chem.* **1992**, *57*, 1643.

[115] a) Kitagawa, O., Aoki, K., Inoue, T., Taguchi, T.; *Tetrahedron Lett.* **1995**, *36*, 593; b) Kitagawa, O., Izawa, H., Taguchi, T., *Tetrahedron Lett.* **1997**, *38*, 4447; c) Kitagawa, O., Izawa, H., Sato, K., Dobashi, A., Taguchi, T., Shiro, M.; *J. Org. Chem.* **1998**, *63*, 2634.

[116] a) Evans, D. A., Miller, S. J., Lectka, T.; *J. Am. Chem. Soc.* **1993**, *115*, 6460; b) Evans, D. A., Murray, J. A., von Matt, P., Norcross, R. D., Miller, S. J.; *Angew. Chem. Int. Ed. Engl.* **1995**, *107*, 798.

[117] Evans, D. A., Burgey, C. S., Paras, N. A., Vojkovsky, T., Tregay, W. S.; *J. Am. Chem. Soc.* **1998**, *120*, 5824.

[118] a) Evans, D. A., Kozlowski, M. C., Burgey, C. S., MacMillan, D. W. C.; *J. Am. Chem. Soc.* **1997**, *119*, 7893; b) Evans, D. A., Olhava, E. J., Johnson, J. S., Janey, J. M.; *Angew. Chem Int. Ed. Engl.* **1998**, *37*, 3372.

[119] a) Levin, J. I., Turos, E., Weinreb, S. M.; *Syn. Commun.* **1982**, *12*, 989; b) Williams, J. M., Jobson, R. B., Yasuda, N., Marchesini, G., Dolling, U. H., Grabowski, E. J. J.; *Tetrahedron Lett.* **1995**, *36*, 5461.

[120] Black, P. J., Harris, W., Williams, J. M. J.; *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 4475.

[121] De Graauw, C. F., Peters, J. A., Van Bekkum, H., Huskens, J.; *Synthesis* **1994**, 1007.

[122] Campbell, E. J., Zhou, H., Nguyen S. T.; *Org. Lett.* **2001**, *3*, 2391.

[123] Sasaki, M., Tanino, K., Mityashita, M.; *J. Org. Chem.* **2001**, *66*, 5388.

[124] Kabalka, G. W., Wu, Z., Ju, Y.; *Tetrahedron Lett.* **2001**, *42*, 6239.

[125] Evans Group Home Page; http://daecr1.harvard.edu/pKa/pKa.html.

[126] Still, W. C., Kahn, M., Mitra, A.; *J. Org. Chem.* **1978**, *43*, 2923.

[127] Maruoka, K., Concepcoin, A. B., Yamamoto, H.; *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3501.

[128] Serra, A. C., de Silva Corrêa, C. M. M., do Vale, M. L. C.; *Tetrahedron*, **1991**, *47*, 9463.

[129] Ranu, B. C., Dutta, J., Guchhait, S. K.; *J. Org. Chem.* **2001**, *66*, 5624.

[130] Fay, C. K., Grutzner, J. B., Johnson, L. F., Sternhell, S., Westerman, P. W.; *J. Org. Chem.* **1973**, *38*, 3122.

[131] Gössinger, E., Müller, R.; *Tetrahedron Lett.* **1989**, *45*, 1377.

[132] Chung, Y., Duerr, B. F., McKelvey, T. A., Nanjappan, P., Czarnik, A. W.; *J. Org. Chem.* **1989**, *54*, 1018.

[133] Womack, E. B., McWhirter, J.; *Organic Syntheses;* Wiley: New York, **1955**, *Coll. Vol. III*, 714.

[134] Jabin, I., Revial, G., Tomas, A., Lemoiné, P., Pfau, M.; *Tetrahedron: Asymmetry* **1995**, *6*, 1795.

[135] Kanemasa, S., Oderaotoshi, Y., Sakaguchi, S., Yamamoto, H., Tanaka, J., Wanda, E., Curran, D. P.; *J. Am. Chem. Soc.* **1998**, *120*, 3074.

[136] Evans, D. A., Barnes, D. M., Johnson, J. S., Lectka, T., von Matt, P., Miller, S. J., Murray, J. A., Norcross, R. D., Shaughnessy, E. A., Campos, K. R.; *J. Am. Chem. Soc.* **1999**, *121*, 7582.

[137] Kise, N., Kumada, K., Terao, Y., Ueda, N.; *Tetrahedron* **1998**, *54*, 2697.

[138] Mundy, B. P., Kim, Y.; *J. Heterocyclic Chem.* **1982**, *19*, 1221.

[139] Archibald, S. C., Fleming, I.; *J. Chem. Soc., Perkin Trans. 1* **1993**, 751.

[140] Togo, H., Nabana, T., Yamaguchi, K.; *J. Org. Chem.* **2000**, *65*, 8391.

[141] Caddick, S., Afonso, C. A. M., Candeias, S. X., Hitchcock, P. B., Jenkins, K., Murtagh, L., Pardoe, D., Santos, A. G., Treweeke, N. R., Weaving, R.; *Tetrahedron* **2001**, *57*, 6589.

[142] Rhee, H., Kim, J. Y.; *Tetrahedron Lett.* **1998**, *39*, 1365.

[143] Nicolas, L., Beugelmans-Verrier, M., Gulhem, J.; *Tetrahedron* **1981**, *37*, 3847.

[144] Degani, I., Dughera, S., Fochi, R., Serra, E.; *Synthesis* **1999**, 1200.

[145] Kim, S., Lee, J. I.; *J. Org. Chem.* **1984**, *49*, 1712.

[146] Solladie, G., Gehrold, N., Maignan, J.; *Eur. J. Org. Chem.* **1999**, 2309.

[147] Dinwiddie, J. G., McManus, S. P.; *J. Org. Chem.* **1965**, *30*, 766.

[148] Bradsher, C. K., Wissow, L. J.; *J. Am. Chem. Soc.* **1946**, *68*, 2149.

[149] Dawson, G. J., Williams, J. M. J., Coote, S. J., *Tetrahedron: Asymmetry* **1995**, *6*, 2535.

[150] On completion of this thesis, a report was published detailing the cycloaddition of N-alkoxyacrylamides catalysed by Et_2Zn or $AlMe_3$. Me_2AlCl was found to be an inefficient catalyst, resulting in only decomposition of the starting acrylates. Corminbouef, O., Renaud, P.; *Org. Lett.* **2002**, *4*, 1735.

Chapter 7

Appendices

Appendix 1

Independent Reactions for formation of 89 and 90

Both reactions were run at a concentration of 0.5 M. Prior calibration with known standard samples allowed for determination of real percentage conversions from observed conversions.

Table 23: Conversion for formation of **89** and **90**

Time	% 89	% 90
0	0	0
15	18.1	2.8
45	53.6	7.7
75	72.8	13.2
100	80.9	
105		18.8
135	87.9	21.6
165	91.6	25.8
195	94.6	28.4
225	95.3	34.2
255	96.5	33.3
285	97.4	39.1
315		44.6
400		46.0

This data allows for the calculation of the rate constant for the reactions.

Formation of **89**: k = 0.0149 (Relative rate = 1000)

Formation of **90**: k = 0.0017 (Relative rate = 114)

1:1 Competition reaction for formation of 89 vs 90

The concentration of both reactants was 0.5 M. Prior calibration with known standard samples allowed for determination of real percentage conversions from observed conversions.

Table 24: Conversion for 1:1 competition reaction for formation of **89** vs **90**

Time	% 89	% 90
0	0	0
15	0.5	5.1
45	1.7	14.2
70	3.4	23.2
95	5.0	31.4
120	6.1	35.4
145	7.7	41.5
170	8.3	44.1
195	10.5	49.1
220	12.0	53.3
245	12.9	56.8
275	16.0	64.6
300	18.0	65.0
325	18.5	66.9
350	20.0	68.5
375	20.1	69.7
400	23.9	74.1

This data allows for the calculation of the rate constant for the reactions.

Formation of **89**: k = 0.0006 (Relative rate = 40)

Formation of **90**: k = 0.0035 (Relative rate = 235)

1:2 Competition reaction for formation of 89 vs 90

The concentration of both reactants was 0.5 M. Prior calibration with known standard samples allowed for determination of real percentage conversions from observed conversions.

Table 25: Conversion for 1:2 competition reaction for formation of **89** vs **90**

Time	% 89	% 90
0	0	0
15	0.4	5.7
40	0.7	10.0
65	1.4	15.0
90	1.4	16.6
115	2.3	26.3
140	2.5	26.6
165	3.0	29.6
190	3.9	34.8
215	4.8	38.6
240	6.4	43.1
265	5.1	41.5
290	8.2	53.2
315	8.1	51.5
340	6.4	47.3
365	5.8	46.2
390	7.9	53.8

This data allows for the calculation of the rate constant for the reactions.

Formation of **89**: k = 0.0002 (Relative rate = 13)

Formation of **90**: k = 0.0021 (Relative rate = 141)

Appendix 2

Crystallographic Data for palladium complex $Pd(dba)(PPh_3)_2$

Table 26: Crystal data and structure refinement for $Pd(dba)(PPh_3)_2$

Empirical formula	C53 H44 O P2 Pd
Formula weight	865.22
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.7810(1)Å α = 100.790(1)°
	b = 11.7020(1)Å β = 96.690(1)°
	c = 17.5250(2)Å γ = 94.774(1)°
Volume	2144.50(4) $Å^3$
Z	2
Density (calculated)	1.340 Mg/m^3
Absorption coefficient	0.546 mm^{-1}
F(000)	892
Crystal size	0.30 x 0.25 x 0.25 mm
Theta range for data collection	3.53 to 30.02°
Index ranges	-15<=h<=15; -16<=k<=16; -24<=l<=24
Reflections collected	45678
Independent reflections	12481 [R(int) = 0.0332]
Reflections observed (>2σ)	11302
Data Completeness	0.995
Max. and min. transmission	0.8757 and 0.8534
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12481 / 0 / 515
Goodness-of-fit on F^2	1.018
Final R indices [I>2σ(I)]	R_1 = 0.0252 wR_2 = 0.0660
R indices (all data)	R_1 = 0.0300 wR_2 = 0.0688
Largest diff. peak and hole	0.599 and -0.517 $eÅ^{-3}$

Table 27: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for $Pd(dba)(PPh_3)_2$. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

Atom	x	y	z	U(eq)
Pd(1)	7306(1)	2836(1)	2784(1)	16(1)
P(1)	8831(1)	2726(1)	1930(1)	21(1)
P(2)	7882(1)	2261(1)	3966(1)	16(1)
O(7)	6294(1)	5450(1)	2926(1)	32(1)
C(1)	8239(1)	2858(1)	923(1)	24(1)
C(2)	7093(2)	2220(2)	587(1)	31(1)
C(3)	6571(2)	2277(2)	-170(1)	42(1)

C(4)	7199(2)	2962(2)	-597(1)	44(1)
C(5)	8342(2)	3579(2)	-277(1)	42(1)
C(6)	8869(2)	3526(1)	481(1)	33(1)
C(7)	10156(1)	3874(1)	2199(1)	25(1)
C(8)	9888(2)	5032(1)	2252(1)	33(1)
C(9)	10843(2)	5951(2)	2483(1)	41(1)
C(10)	12066(2)	5727(2)	2680(1)	42(1)
C(11)	12341(2)	4585(2)	2640(1)	39(1)
C(12)	11395(1)	3657(2)	2395(1)	31(1)
C(13)	9539(1)	1350(1)	1712(1)	23(1)
C(14)	9276(2)	486(1)	2127(1)	33(1)
C(15)	9745(2)	-591(2)	1956(1)	41(1)
C(16)	10478(2)	-814(2)	1361(1)	36(1)
C(17)	10743(2)	42(2)	940(1)	36(1)
C(18)	10280(2)	1120(2)	1107(1)	33(1)
C(19)	9389(1)	2911(1)	4532(1)	19(1)
C(20)	10457(1)	2830(1)	4157(1)	28(1)
C(21)	11635(1)	3283(2)	4562(1)	35(1)
C(22)	11751(1)	3844(1)	5339(1)	30(1)
C(23)	10694(1)	3982(1)	5704(1)	29(1)
C(24)	9515(1)	3507(1)	5310(1)	24(1)
C(25)	7948(1)	683(1)	3828(1)	19(1)
C(26)	6898(1)	-14(1)	3381(1)	22(1)
C(27)	6862(1)	-1222(1)	3224(1)	26(1)
C(28)	7876(2)	-1756(1)	3499(1)	31(1)
C(29)	8916(2)	-1075(1)	3942(1)	36(1)
C(30)	8958(2)	145(1)	4107(1)	28(1)
C(31)	6802(1)	2483(1)	4703(1)	18(1)
C(32)	6407(1)	3594(1)	4908(1)	22(1)
C(33)	5594(1)	3812(1)	5465(1)	25(1)
C(34)	5137(1)	2919(1)	5812(1)	28(1)
C(35)	5521(2)	1815(1)	5610(1)	30(1)
C(36)	6359(1)	1597(1)	5066(1)	25(1)
C(37)	4601(1)	1955(1)	2857(1)	25(1)
C(38)	4032(1)	1754(2)	3504(1)	32(1)
C(39)	3321(2)	703(2)	3485(1)	44(1)
C(40)	3159(2)	-169(2)	2824(1)	51(1)
C(41)	3715(2)	12(2)	2176(1)	46(1)
C(42)	4429(2)	1057(1)	2188(1)	32(1)
C(43)	5364(1)	3079(1)	2902(1)	21(1)
C(44)	5675(1)	3498(1)	2236(1)	21(1)
C(45)	6100(1)	4733(1)	2296(1)	22(1)
C(46)	6265(1)	5106(1)	1543(1)	24(1)
C(47)	6507(2)	6230(1)	1516(1)	27(1)
C(48)	6655(1)	6744(1)	826(1)	28(1)
C(49)	6899(2)	7955(2)	922(1)	38(1)
C(50)	7046(2)	8476(2)	285(1)	47(1)
C(51)	6952(2)	7793(2)	-458(1)	44(1)
C(52)	6714(2)	6589(2)	-563(1)	40(1)
C(53)	6560(2)	6065(2)	71(1)	33(1)

Table 28: Bond lengths (Å) and angles (°) for $Pd(dba)(PPh_3)_2$

Pd(1)-C(43)	2.1646(12)	Pd(1)-C(44)	2.1744(12)
Pd(1)-P(2)	2.3295(3)	Pd(1)-P(1)	2.3425(3)
P(1)-C(7)	1.8309(15)	P(1)-C(13)	1.8345(14)
P(1)-C(1)	1.8455(14)	P(2)-C(25)	1.8252(13)
P(2)-C(19)	1.8271(13)	P(2)-C(31)	1.8342(13)
O(7)-C(45)	1.2395(16)	C(1)-C(6)	1.390(2)
C(1)-C(2)	1.394(2)	C(2)-C(3)	1.394(2)
C(3)-C(4)	1.383(3)	C(4)-C(5)	1.375(3)
C(5)-C(6)	1.397(2)	C(7)-C(12)	1.396(2)
C(7)-C(8)	1.397(2)	C(8)-C(9)	1.391(2)
C(9)-C(10)	1.383(3)	C(10)-C(11)	1.383(3)
C(11)-C(12)	1.394(2)	C(13)-C(14)	1.382(2)
C(13)-C(18)	1.3994(19)	C(14)-C(15)	1.391(2)
C(15)-C(16)	1.381(2)	C(16)-C(17)	1.380(3)
C(17)-C(18)	1.389(2)	C(19)-C(20)	1.3918(19)
C(19)-C(24)	1.3962(18)	C(20)-C(21)	1.390(2)
C(21)-C(22)	1.383(2)	C(22)-C(23)	1.378(2)
C(23)-C(24)	1.3909(19)	C(25)-C(30)	1.3877(19)
C(25)-C(26)	1.4002(18)	C(26)-C(27)	1.3845(19)
C(27)-C(28)	1.386(2)	C(28)-C(29)	1.382(2)
C(29)-C(30)	1.398(2)	C(31)-C(36)	1.3933(18)
C(31)-C(32)	1.3981(18)	C(32)-C(33)	1.3890(19)
C(33)-C(34)	1.388(2)	C(34)-C(35)	1.384(2)
C(35)-C(36)	1.3932(19)	C(37)-C(38)	1.399(2)
C(37)-C(42)	1.403(2)	C(37)-C(43)	1.475(2)
C(38)-C(39)	1.386(2)	C(39)-C(40)	1.376(3)
C(40)-C(41)	1.385(3)	C(41)-C(42)	1.386(2)
C(43)-C(44)	1.4117(18)	C(44)-C(45)	1.460(2)
C(45)-C(46)	1.4898(19)	C(46)-C(47)	1.331(2)
C(47)-C(48)	1.466(2)	C(48)-C(49)	1.395(2)
C(48)-C(53)	1.398(2)	C(49)-C(50)	1.387(2)
C(50)-C(51)	1.381(3)	C(51)-C(52)	1.384(3)
C(52)-C(53)	1.385(2)		
C(43)-Pd(1)-C(44)	37.97(5)	C(43)-Pd(1)-P(2)	98.96(4)
C(44)-Pd(1)-P(2)	136.39(4)	C(43)-Pd(1)-P(1)	145.30(4)
C(44)-Pd(1)-P(1)	108.43(4)	P(2)-Pd(1)-P(1)	115.174(12)
C(7)-P(1)-C(13)	105.28(7)	C(7)-P(1)-C(1)	102.38(7)
C(13)-P(1)-C(1)	99.28(6)	C(7)-P(1)-Pd(1)	115.52(4)
C(13)-P(1)-Pd(1)	117.89(5)	C(1)-P(1)-Pd(1)	114.20(5)
C(25)-P(2)-C(19)	105.11(6)	C(25)-P(2)-C(31)	101.02(6)
C(19)-P(2)-C(31)	102.38(6)	C(25)-P(2)-Pd(1)	111.70(4)
C(19)-P(2)-Pd(1)	117.53(4)	C(31)-P(2)-Pd(1)	117.13(4)
C(6)-C(1)-C(2)	118.71(14)	C(6)-C(1)-P(1)	124.42(12)
C(2)-C(1)-P(1)	116.86(11)	C(3)-C(2)-C(1)	120.62(16)
C(4)-C(3)-C(2)	119.96(17)	C(5)-C(4)-C(3)	119.93(15)
C(4)-C(5)-C(6)	120.41(17)	C(1)-C(6)-C(5)	120.34(16)

C(12)-C(7)-C(8)	118.78(14)	C(12)-C(7)-P(1)	123.64(12)
C(8)-C(7)-P(1)	117.47(11)	C(9)-C(8)-C(7)	120.61(15)
C(10)-C(9)-C(8)	120.12(17)	C(11)-C(10)-C(9)	119.84(16)
C(10)-C(11)-C(12)	120.47(16)	C(11)-C(12)-C(7)	120.16(16)
C(14)-C(13)-C(18)	118.82(13)	C(14)-C(13)-P(1)	118.97(10)
C(18)-C(13)-P(1)	122.10(11)	C(13)-C(14)-C(15)	120.94(14)
C(16)-C(15)-C(14)	120.07(16)	C(15)-C(16)-C(17)	119.47(15)
C(16)-C(17)-C(18)	120.86(14)	C(17)-C(18)-C(13)	119.84(15)
C(20)-C(19)-C(24)	118.69(12)	C(20)-C(19)-P(2)	117.91(10)
C(24)-C(19)-P(2)	123.37(10)	C(21)-C(20)-C(19)	120.59(14)
C(22)-C(21)-C(20)	120.09(15)	C(23)-C(22)-C(21)	119.84(14)
C(22)-C(23)-C(24)	120.42(14)	C(23)-C(24)-C(19)	120.25(13)
C(30)-C(25)-C(26)	118.97(12)	C(30)-C(25)-P(2)	125.19(10)
C(26)-C(25)-P(2)	115.81(10)	C(27)-C(26)-C(25)	120.58(13)
C(26)-C(27)-C(28)	120.30(14)	C(29)-C(28)-C(27)	119.50(14)
C(28)-C(29)-C(30)	120.63(14)	C(25)-C(30)-C(29)	120.01(14)
C(36)-C(31)-C(32)	118.64(12)	C(36)-C(31)-P(2)	123.10(10)
C(32)-C(31)-P(2)	118.26(10)	C(33)-C(32)-C(31)	120.64(13)
C(32)-C(33)-C(34)	120.33(13)	C(35)-C(34)-C(33)	119.40(13)
C(34)-C(35)-C(36)	120.55(14)	C(35)-C(36)-C(31)	120.41(13)
C(38)-C(37)-C(42)	117.68(14)	C(38)-C(37)-C(43)	119.65(13)
C(42)-C(37)-C(43)	122.66(13)	C(39)-C(38)-C(37)	121.15(16)
C(40)-C(39)-C(38)	120.47(17)	C(39)-C(40)-C(41)	119.40(17)
C(40)-C(41)-C(42)	120.69(18)	C(41)-C(42)-C(37)	120.61(16)
C(44)-C(43)-C(37)	123.40(12)	C(44)-C(43)-Pd(1)	71.39(7)
C(37)-C(43)-Pd(1)	111.66(9)	C(43)-C(44)-C(45)	120.49(12)
C(43)-C(44)-Pd(1)	70.64(7)	C(45)-C(44)-Pd(1)	102.93(9)
O(7)-C(45)-C(44)	123.20(13)	O(7)-C(45)-C(46)	120.85(13)
C(44)-C(45)-C(46)	115.94(11)	C(47)-C(46)-C(45)	121.13(12)
C(46)-C(47)-C(48)	128.03(13)	C(49)-C(48)-C(53)	118.40(14)
C(49)-C(48)-C(47)	119.12(14)	C(53)-C(48)-C(47)	122.48(14)
C(50)-C(49)-C(48)	120.90(17)	C(51)-C(50)-C(49)	120.01(18)
C(50)-C(51)-C(52)	119.82(16)	C(51)-C(52)-C(53)	120.41(17)
C(52)-C(53)-C(48)	120.47(16)		

Table 29: Anisotropic displacement parameters ($Å^2$ x 10^3) for $Pd(dba)(PPh_3)_2$. The anisotropic displacement factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11+...2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
Pd(1)	17(1)	18(1)	16(1)	4(1)	4(1)	4(1)
P(1)	19(1)	25(1)	18(1)	3(1)	5(1)	4(1)
P(2)	17(1)	16(1)	17(1)	4(1)	3(1)	3(1)
O(7)	50(1)	25(1)	21(1)	1(1)	7(1)	7(1)
C(1)	26(1)	28(1)	19(1)	1(1)	5(1)	9(1)
C(2)	28(1)	37(1)	24(1)	-3(1)	3(1)	6(1)
C(3)	36(1)	53(1)	29(1)	-9(1)	-4(1)	14(1)
C(4)	63(1)	47(1)	22(1)	1(1)	-3(1)	26(1)
C(5)	69(1)	37(1)	24(1)	10(1)	10(1)	12(1)
C(6)	42(1)	33(1)	25(1)	7(1)	7(1)	4(1)

C(7)	23(1)	32(1)	19(1)	3(1)	6(1)	1(1)
C(8)	31(1)	32(1)	33(1)	2(1)	3(1)	2(1)
C(9)	45(1)	32(1)	42(1)	3(1)	3(1)	-3(1)
C(10)	36(1)	47(1)	36(1)	1(1)	2(1)	-13(1)
C(11)	25(1)	56(1)	33(1)	3(1)	1(1)	-3(1)
C(12)	25(1)	41(1)	26(1)	5(1)	4(1)	4(1)
C(13)	21(1)	28(1)	22(1)	3(1)	5(1)	6(1)
C(14)	37(1)	32(1)	33(1)	7(1)	17(1)	10(1)
C(15)	48(1)	31(1)	50(1)	13(1)	22(1)	13(1)
C(16)	35(1)	32(1)	40(1)	1(1)	9(1)	13(1)
C(17)	36(1)	44(1)	33(1)	3(1)	15(1)	17(1)
C(18)	35(1)	38(1)	31(1)	10(1)	15(1)	14(1)
C(19)	19(1)	17(1)	21(1)	6(1)	1(1)	2(1)
C(20)	23(1)	34(1)	28(1)	5(1)	6(1)	2(1)
C(21)	21(1)	43(1)	44(1)	12(1)	6(1)	1(1)
C(22)	26(1)	25(1)	39(1)	15(1)	-7(1)	-5(1)
C(23)	33(1)	24(1)	26(1)	5(1)	-6(1)	-1(1)
C(24)	27(1)	22(1)	22(1)	3(1)	1(1)	4(1)
C(25)	24(1)	17(1)	17(1)	4(1)	4(1)	3(1)
C(26)	22(1)	20(1)	24(1)	3(1)	5(1)	2(1)
C(27)	32(1)	21(1)	22(1)	2(1)	7(1)	-2(1)
C(28)	50(1)	18(1)	27(1)	6(1)	4(1)	5(1)
C(29)	48(1)	22(1)	35(1)	6(1)	-8(1)	12(1)
C(30)	35(1)	21(1)	27(1)	5(1)	-5(1)	7(1)
C(31)	19(1)	19(1)	17(1)	4(1)	3(1)	3(1)
C(32)	24(1)	19(1)	24(1)	6(1)	5(1)	4(1)
C(33)	28(1)	24(1)	26(1)	4(1)	7(1)	9(1)
C(34)	29(1)	31(1)	25(1)	6(1)	12(1)	7(1)
C(35)	36(1)	27(1)	32(1)	11(1)	17(1)	4(1)
C(36)	31(1)	21(1)	27(1)	8(1)	11(1)	6(1)
C(37)	17(1)	32(1)	26(1)	10(1)	0(1)	5(1)
C(38)	21(1)	42(1)	35(1)	13(1)	5(1)	3(1)
C(39)	31(1)	58(1)	47(1)	25(1)	3(1)	-8(1)
C(40)	44(1)	50(1)	55(1)	23(1)	-9(1)	-20(1)
C(41)	50(1)	39(1)	41(1)	7(1)	-13(1)	-10(1)
C(42)	32(1)	33(1)	29(1)	7(1)	-3(1)	-1(1)
C(43)	18(1)	26(1)	21(1)	5(1)	3(1)	8(1)
C(44)	22(1)	24(1)	19(1)	4(1)	2(1)	8(1)
C(45)	24(1)	24(1)	20(1)	5(1)	3(1)	9(1)
C(46)	28(1)	26(1)	19(1)	3(1)	1(1)	6(1)
C(47)	36(1)	25(1)	21(1)	4(1)	4(1)	5(1)
C(48)	27(1)	30(1)	27(1)	10(1)	2(1)	4(1)
C(49)	46(1)	33(1)	37(1)	11(1)	4(1)	-2(1)
C(50)	49(1)	43(1)	54(1)	26(1)	4(1)	-6(1)
C(51)	33(1)	65(1)	42(1)	33(1)	2(1)	-2(1)
C(52)	34(1)	62(1)	27(1)	17(1)	3(1)	5(1)
C(53)	37(1)	37(1)	26(1)	10(1)	4(1)	6(1)

Table 30: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for $Pd(dba)(PPh_3)_2$

Atom	x	y	z	U(eq)
H(2)	6663	1742	876	37
H(3)	5786	1846	-392	50
H(4)	6842	3007	-1111	53
H(5)	8775	4043	-573	51
H(6)	9662	3949	695	40
H(8)	9047	5193	2129	39
H(9)	10654	6734	2505	49
H(10)	12715	6356	2844	50
H(11)	13180	4433	2780	47
H(12)	11594	2875	2362	37
H(14)	8768	630	2536	39
H(15)	9561	-1175	2250	49
H(16)	10798	-1550	1242	43
H(17)	11249	-109	531	43
H(18)	10465	1701	811	39
H(20)	10381	2461	3620	34
H(21)	12360	3207	4304	42
H(22)	12558	4133	5620	36
H(23)	10770	4405	6229	34
H(24)	8794	3587	5571	29
H(26)	6204	345	3184	26
H(27)	6140	-1686	2926	31
H(28)	7856	-2584	3385	38
H(29)	9609	-1439	4135	43
H(30)	9677	605	4411	34
H(32)	6697	4206	4664	26
H(33)	5350	4575	5609	30
H(34)	4567	3064	6184	33
H(35)	5209	1200	5845	36
H(36)	6630	841	4941	30
H(38)	4133	2347	3964	38
H(39)	2943	584	3931	53
H(40)	2670	-887	2812	61
H(41)	3605	-588	1718	55
H(42)	4806	1167	1740	39
H(43)	5662	3544	3405	26
H(44)	5606	2973	1745	26
H(46)	6196	4531	1075	29
H(47)	6596	6766	2003	33
H(49)	6966	8430	1431	46
H(50)	7212	9302	359	57
H(51)	7050	8149	-895	53
H(52)	6656	6119	-1073	48
H(53)	6388	5239	-8	39
H(2)	6663	1742	876	37
H(3)	5786	1846	-392	50
H(4)	6842	3007	-1111	53

H(5)	8775	4043	-573	51
H(6)	9662	3949	695	40
H(8)	9047	5193	2129	39
H(9)	10654	6734	2505	49
H(10)	12715	6356	2844	50

Appendix 3

GC rate data for the formation of 115

The rate of formation of **115** was followed by GC analysis using Dodecane as an internal standard. A calibration sample containing equimolar amounts of methyl acrylate **114** and dodecane (conc.= 0.5 M) was analysed. The ratio of the areas of the two peaks gave a calibration constant z = 1.83. Using this constant, the concentration of starting material can be determined using **Equation 2** which in turn allows calculation of the percentage conversion.

$$[SM]_t = z(AreaSM)[IS]/AreaIS$$

Equation 2

Table 31: Rate of formation of **115**

Time	% Conversion
0	0
15	17.9
60	26.3
105	40.2
150	41.2
195	47.2
240	51.8
285	59.6
335	63.1
375	68.2
420	69.7

This enables the rate constant for the reaction to be determined.

Formation of **115**: k = 0.0031 (Relative rate = 208)

HPLC rate data for the formation of 117

The of formation of **117** was followed by HPLC analysis following prior calibration with known standards. Samples containing 10, 50, 100, 150 and 300μg/ml of starting

material and product were analysed. At such low concentration the relationship between concentration and absorbance is approximately linear. The ratio of the gradients, y, can be calculated from this data and was found to be 2.8. During the reaction percentage conversion can be determined using **Equation 3** which in turn allows calculation of the percentage conversion.

$$\% \text{ Conversion} = (\text{AreaP/MwP})/\{(\text{AreaP/MwP})+((\text{AreaSM/y})/\text{MwSM})\}$$

Equation 3

Table 32: Rate of formation of **117**

Time	% Conversion
0	0
10	38.3
45	87.8
85	97.2
125	99.5
160	99.9
195	100

This enables the rate constant for the reaction to be determined.

Formation of **117**: k = 0.0429 (Relative rate = 2879)